

Decision Algorithms for Emergency Neurology

Giuseppe Micieli
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Foreword

In the last years, Neurology had an impressive advancement in its numerous areas with an improvement of the knowledge of the diseases' mechanisms and, consequently, of the therapies that are now available to treat and even to cure a number of disorders of the central and peripheral nervous system. Neurologists now can make a precise diagnosis, using their clinical capacities magnified by the relevant advancements of neuroradiology and other laboratory tests and are now able to treat diseases that a few decades ago they could only diagnose and carefully observe such as multiple sclerosis, cerebrovascular disorders, headache, epilepsy, extrapyramidal diseases, and many other disturbances. This is particularly true especially for the neurological emergencies, which often can be successfully treated, if a precise diagnosis is done in a short period of time. Medical emergencies may be quite different, according to the affected organ, and therefore the first and most important point in a context of an emergency is to have the capacity to arrive at a precise diagnosis. The neurologist has the knowledge to differentiate a functional from an organic problem, a loss of strength due to a cerebrovascular disorder from other numerous possible causes, a confusional condition due to an epileptic status from a metabolic disorder, and so on, and subsequently establish the more appropriate treatment. The Association of Italian Neurologists dedicated to the neurological emergencies (ANEU), Association that is strictly joined to the Italian Neurological Society (SIN) that covers all the different and numerous fields of the Neurological Clinical Sciences, is dedicated to face the numerous and complex aspects of the neurological

emergencies, from a diagnostic and therapeutic point of view, and also offering organizational models that are compatible with our Health National System. One of the most important merit of the present textbook on “Decision Algorithms for Emergency Neurology” is that it clearly describes that a neurological emergency can be treated only after a clear-cut diagnosis has been carried out, and that this task is reserved to the neurologists. The Manual has also the important value to offer a complete overview on the most relevant advancement in the treatment of the neurological emergencies, contributing to the process of education of a modern neurologist that has the capacity to face the numerous and difficult problems of the diseases of the nervous system.

Genova, Italy
Naples, Italy
February 3, 2020

Gianluigi Mancardi
Giacchino Tedeschi

Preface

I must begin with a confession: When I finished medical school in 1978 and then residency training in 1981, I “hated” neurology. I was not just uninterested but I actively hated it. Why?

My teachers of neurology trained in another era. They would ask an endless series of questions and then conduct a seemingly interminable neurological exam in great detail. Then we would need to listen to them wax eloquently about the localization of the lesion and its probable cause. At the end of this clinical exercise, when it came to the treatment, more often than not the teacher would throw up their hands and shrug their shoulders. Diagnostic testing had major limitations when I was a resident. A non-contrast brain CT scan was a relatively new test that took 30–45 min to do and which produced images were almost always severely degraded by motion artifact. By contrast, modern scanners do the job in less than 10 s and usually generate near perfect quality images. For an action-oriented young physician like myself who preferred the pace of emergency medicine, it was boring. The pathology causing these acute neurological symptoms was often admired in the autopsy room, rather than treated in the emergency department (ED) or wards.

Fast forward to 2020, after nearly 40 years of practice in the ED and I now find myself a card-carrying “neuro-phile.” How do I account for this transition?

About 30 years ago, I saw a patient in the ED with acute neck pain that turned out to have an aneurysmal subarachnoid hemorrhage. No headache—just neck pain. In retrospect, I stumbled on the correct diagnosis more by luck than

by skill, but this one patient stimulated my interest in acute neurology, in subarachnoid hemorrhage and in misdiagnosis in general. My “hate” became “interest,” and over time, my “interest” matured into “passion.” Over the past four decades, we have acquired more high-quality data, developed far more accurate diagnostic tests, and increasingly, we have more evidence-based effective treatments for these patients.

In most general EDs, approximately 5–8% of patients present for evaluation of various neurological complaints including headache, neck, and back pain, focal or generalized weakness, alterations in level of consciousness, dizziness, visual and sensory symptoms, and seizure. Many of these patients will have benign and self-limiting conditions; however, a significant minority will have serious illnesses whose treatments are time critical. Is the headache due to a migraine ... or a subarachnoid hemorrhage? Is the back pain a simple disc protrusion ... or an epidural abscess? Or the dizzy patient—do they have vestibular neuritis ... or a cerebellar stroke?

These questions and other similar ones arise on a daily basis in most busy ED. Correct and timely diagnosis will increase the odds of a good patient-centered outcome. On the other hand, a misdiagnosis often leads to poor outcomes that affect the patient, their family, and society at large for years and decades not to mention the negative psychological impact that they have on the physicians and nurses involved.

The primary tools that clinicians have at their disposal to effectively distinguish patients with benign conditions from those with serious ones are a careful history and targeted physical examination both done and interpreted through the lens of their knowledge of anatomy, normal physiology, and pathophysiology. This knowledge informs how the physical examination is done, which components should receive special emphasis and how the findings are interpreted. Although this is true for all patients, I think that this is more true in patients with neurological problems.

Over the last 20–30 years, an incredibly accurate array of newer diagnostic tests have been developed, but which

patients need which tests? Knowledge of the indications for and limitations of the expanding menu of brain and spine imaging examinations inform the choice and timing of performing these diagnostic studies and finally how to interpret the results. For example, in patients with thunderclap headache, a non-contrast head CT scanning is so accurate when done within 6 h of the headache onset that its sensitivity approaches 100% rendering a lumbar puncture of little value in these early-presenting patients. On the other hand, MRI, even with diffusion-weighted sequences, may be falsely negative in the first 48 h in patients presenting with acute dizziness from an acute vestibular syndrome due to stroke. In fact, a careful targeted physical examination is more accurate.

In addition, we simply have more data, more evidence upon which to make clinical decisions. For decades, very little new information contributed to our evidence base for intracerebral hemorrhage (ICH). Now large cooperative multicenter studies better inform blood pressure targets for these patients. Newer treatment modalities such as minimally invasive surgery are being studied. We now have four-factor prothrombin complex concentrates to reverse warfarin-associated ICH and other new specific reversal agents for the newer direct anti-thrombin and anti-Xa anticoagulants.

Regarding intracranial aneurysms, the treatment paradigm has totally shifted from open surgical procedures being performed in nearly all patients to the use of endovascularly deployed coils. And as newer devices are developed to “shape” the parent vessel, an increasing proportion of aneurysms have become amenable to this far less-invasive treatment. Other problems such as vasospasm prevention and treatment remain more problematic.

Acute ischemic stroke care has been completely transformed. When I was a trainee, an acute stroke admission was a very minor and rather unexciting event; there was very little to do. Now, an acute stroke creates a whirlwind of activity that requires a series of minute-to-minute attention and interventions. Newer studies emerge on a regular basis that continually change what treatments are available and their

effective time windows. These newer data not only influence which patients are treated and when but also **where** they are treated. Increasingly sophisticated endovascular procedures are currently only available at large medical centers, which affects the point-of-entry for patients with acute focal weakness. This in turn impacts how we deliver prehospital services and forces us to reevaluate our overall systems of care. Where should the ambulance take that patient with acute right-sided weakness? To the nearest peripheral hospital? Or to the regional medical center? GPS-enabled smart phone apps are being developed and tested to help prehospital providers rapidly make these on-the-spot decisions that are tailored to the precise location of the patient and the relative locations of the nearest small and large hospitals.

Few comparative drug studies of status epilepticus existed in the past, and our choices were largely driven by local tradition and habit rather than data. Increasingly, the evidence base has expanded, as has the menu of potentially useful anticonvulsant drugs. As for seizure monitoring (both for non-convulsive status epilepticus and for patients who have received paralytic agents after a grand mal convulsion), until about 10 years ago, I almost never ordered an EEG in the ED because in actual practice, it was not available to me. In the last 10 years however, I routinely will start an ED patient on EEG monitoring using portable equipment knowing that an epileptologist will be monitoring the brain waves remotely.

Although we thought we knew a lot about minor traumatic brain injury, once again, our evidence base was thin. That has substantially evolved. My threshold to obtain a CT scan in these patients has risen dramatically, in part due to increasing recognition about the harm of radiation exposure, especially in young individuals, and also because of very large well-done prospective studies that far better inform exactly who does and who does not benefit from a CT. All of this context allows me to have a much more sophisticated and data-driven conversation with patients and their families about why a CT scan is indicated or not and allows me to allay their fears and anxiety in the latter case.

All of these topics and more are the reasons that this new English language edition of *Neurological Emergencies* is so relevant and important. Other topics that the book covers include special situations such as neurological problems in pregnant and postpartum women, airway issues that occur in patients with acute neurological emergencies, the intersection between toxicology and acute neurology, and of increasing importance in our multidisciplinary world, how we organize the care for these patient, and how emergency physicians and neurologists can better cooperate with one another.

Looking back, I realize now that although a part of my initial feelings about neurological emergencies had to do with the lack of treatments, a significant part had to do with my own knowledge gaps which fed my own fear and insecurities in taking care of this group of patients. Over time, I have made efforts to reduce these gaps, and this has led to a reduction in the fear. Now, I spend a great deal of my time trying to help other physicians to improve their knowledge base and to reduce misdiagnosis. But this is a lifelong quest. As Hippocrates said, "Life is short, art is long ... and judgment difficult." Every physician is, or should be, constantly learning, and this book will help its readers do just that.

Boston, MA, USA

Jonathan A. Edlow

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1. Transient Loss of Consciousness

Giuseppe Micieli, Umberto Aguglia, Francesca Baschieri,
Giovanna Calandra Buonauro, Anna Cavallini,
Pietro Cortelli, and Pietro Guaraldi

Introduction

Transient loss of consciousness (TLoC) is a frequent manifestation in the general population, constituting a significant reason for admission to the emergency room (ER).

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This decision algorithm aims at elucidating the diagnostic process and clinical management of patients presenting with TLoC in the emergency setting.

Definition

TLoC is a condition characterized by real or apparent loss of consciousness of short duration, absence of responsiveness, abnormal motor control, and amnesia for the event [1].

The term TLoC comprises a series of heterogeneous conditions of variable etiologies (traumatic/nontraumatic, cardiogenic/neurogenic/metabolic, etc.).

The diagnostic process includes a timely collection of the anamnesis and an accurate physical examination, with the support, even in acute situations, of instrumental investigations (electrocardiogram, ECG), in order to exclude conditions at greatest risk and rule out differential diagnosis. Further instrumental investigations are often necessary to address and confirm the final diagnosis (tilt test, electroencephalogram-EEG, ECG, blood chemistry, psychodiagnosics interview). The therapeutic approach depends on the multiple differential diagnoses.

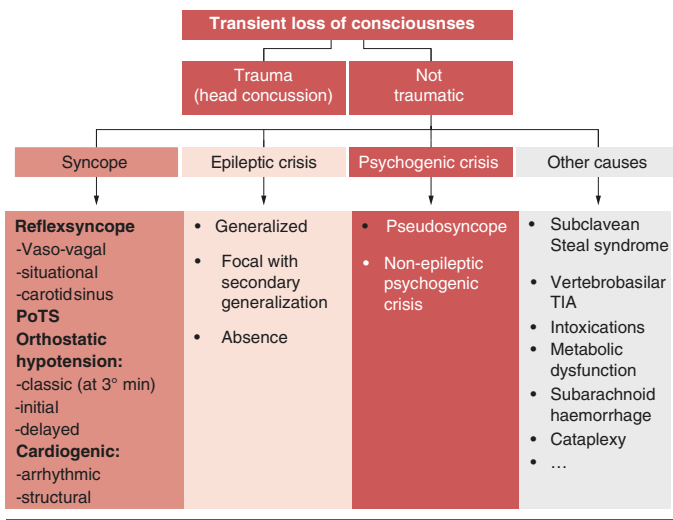
Etiology and Pathophysiology

TLoC can be caused by traumatic and nontraumatic diseases (Fig. 1.1) [1]. This chapter will focus on those of nontraumatic origin, i.e., secondary to cardiological, neurological, and psychogenic dysfunctions. Other conditions (e.g., vascular, toxic-metabolic, etc.) can determine TLoC, but these show further clinical signs in addition to TLoC that are predominant.

The pathophysiology of TLoC varies according to the cause:

- Global cerebral hypoperfusion → syncope
- Hypersynchronous discharge of neuronal groups → epileptic crisis
- Functional disorder → psychogenic crisis

Figure 1.1 TLoC classification



There are different types of syncope depending on the cause of cerebral hypoperfusion [2]:

- Reflex syncope: due to a decrease in sympathetic tone with consequent peripheral vasodilatation and reduction of cardiac output (vasodepressor and cardioinhibitory).
- Orthostatic hypotension: sustained reduction of systolic blood pressure (SBP) by at least -20 mmHg and/or diastolic blood pressure (DBP) by at least -10 mmHg within 3 min of orthostatism. If this drop in blood pressure occurs after 3 min, the orthostatic hypotension is called “delayed.” “Initial” orthostatic hypotension means a transient reduction of SBP >40 mmHg and/or DBP >20 mmHg within 15 s of orthostatism.
- Postural tachycardia syndrome (PoTS): sustained increase in heart rate (HR) ≥ 30 bpm within 10 min of orthostatism or HR >120 bpm in the absence of orthostatic hypotension.
- Cardiogenic syncope: due to structural or arrhythmic abnormalities that affect cardiac function [1].

Diagnosis

Anamnesis

For an adequate diagnostic/prognostic evaluation of TLoC an accurate anamnesis should be collected from patients and *witnesses* (to be contacted by phone, if necessary). With anamnesis alone, syncope can be differentiated from other TLoCs in 60–90% of cases [1, 3].

The medical history must include:

- Family history
- Past medical history
- Medication history
- Circumstances of the event
- Prodromal symptoms and signs
- Characteristics of the ictal phase
- Characteristics of the postictal phase

Each of these items could provide useful elements for the differential diagnosis of TLoC. In particular, some of them are considered “high-risk” factors (🚨) and will be particularly important in patient’s risk stratification. Others have a higher predictive value (✓) for diagnosis. The diagnostic hypothesis and risk stratification guide the management of TLoC patients in the context of acute care (Tables 1.1 and 1.2).

Laboratory and instrumental examinations to be performed in ER [1, 7]:

- 12-leads ECG
- Complete blood panel for anemia, hypoxia, electrolytic and metabolic alterations, intoxications, pulmonary embolism, and cardiac ischemia

Additional laboratory and instrumental tests based on suspected diagnosis [1, 7–9]:

- Cardiac origin: Holter ECG, echocardiogram, ergometric test, electrophysiological study, and *loop recorder*
- Orthostatic hypotension, PoTS: Tilt test

Table 1.1 Differential diagnostic clues obtained from anamnesis

Family history	
Family history of sudden death 🖐️	Long QT syndrome
Past medical history	
Previous TLoC episodes from an early age	Reflex syncope
Heart disease 🖐️	Arrhythmia or structural heart disease
Parkinsonism	Neurogenic orthostachy potension
Epilepsy	Epileptic crisis
Psychiatric disorders	Psychogenic disorder
	Iatrogenic orthostachy potension
Pharmacological history	
Antihypertensive, antianginal, antidepressant, antipsychotic, diuretic, antiarrhythmic, medications for prostate hypertrophy, erectile dysfunction or glaucoma	Iatrogenic orthostachy potension Hypotension secondary to hypovolemia Arrhythmia
Circumstances of the event	
After a meal	Orthostatic hypotension
After head movements, pressure on the neck	Carotid sinus hypersensitivity
Related to fear, pain, stress, urination, defecation, coughing, swallowing	Reflex syncope

Continued

Table 1.1 Continued

During physical exercise 🙌	Cardiogenic syncope
Immediately after the suspension of physical exercise	Orthostatic hypotension
During exercise of the upper limbs	Subclavian steal syndrome
Preceded by sudden and brief palpitations 🙌	Cardiogenic syncope (arrhythmia)
Preceded by a startle (e.g., sudden loud noise) 🙌	Long QT syndrome
Intermittent light stimulation, sleep deprivation	Epileptic crisis
Warm environment	Reflex syncope
	Orthostatic hypotension
Prolonged standing	Reflex syncope
Postural changes	Orthostatic hypotension
In supine position 🙌	Epileptic crisis
	Cardiogenic syncope
Symptoms and prodromal signs	
Nausea, sweating, paleness, blurred vision	Reflex syncope
Lightheadedness /dizziness/confusion, blurred vision, pain in neck and shoulder	Orthostatic hypotension

Table 1.1 Continued

Ascending epigastric sensation, unpleasant smell or taste, <i>déjà vu</i> or <i>jamais vu</i>	Epileptic aura
Beginning with a scream	Epileptic crisis
No symptoms or prodromal signs 🖐	Cardiogenic syncope
	Epileptic crisis
Prolonged prodromal symptoms	Reflex syncope

Characteristics of the critical phase [4–6]

Duration of TLoC	<20 s	Syncope
	1 min	Epileptic crisis
Signs	<i>Morsus</i> *	Epileptic crisis (side of the tongue)
		Syncope (rare; tip of tongue)
	Urinary incontinence	Epileptic crisis
		Syncope
	Fecal incontinence*	Epileptic crisis
	Eyes open/revulsion of the eyes	Epileptic crisis
		Syncope
	Eyes closed*	Pseudosyncope Non-epileptic psychogenic crisis
	Cyanotic face	Epileptic crisis
		Cardiogenic syncope
	Paleness	Reflex syncope
		Orthostatic hypotension

Continued

Table 1.1 Continued

Involuntary movements		
<i>When:</i>	At the beginning or just before TLoC	Epileptic crisis
	After the on set of TLoC	Epileptic crisis
		Syncope
<i>How:</i>	Symmetrical, synchronous, stereotypical	Epileptic crisis
	Asymmetrical, asynchronous, small amplitude	Syncope
	Head version to one side*	Epileptic crisis
	Heterogeneous (non-stereotyped) manifestations	Pseudosyncope
<i>How long</i>	Less than 10 myoclonic jerks	Syncope
	More than 20 myoclonic jerks*	Epilepsy
Characteristics of the post-critical phase		
Nausea, sweating, paleness	Reflex syncope	
Mental lucidity immediately after recovery of consciousness	Syncope	
Confusion/drowsiness	Epileptic crisis	
Muscle pain	Epileptic crisis	
Prolonged asthenia	Syncope	
	Epileptic crisis	

Table 1.1 Continued

	Pseudosyncope	
Objective examination (for all patient [1, 7])		
Blood pressure	Persistent SBP < 90 mmHg 🖐	Cardiogenic syncope
	SBP reduction >20 mmHg and/or DBP >10 mmHg with in 3 min of orthostatism	Orthostatic hypotension
Heart rate	Persistent bradycardia <40 bp min the absence of physical training 🖐	Cardiogenic syncope
	Bradycardia	Reflex syncope
	Increase HR >30b pm and/or HR >120b pm within 10 min of orthostatic work	PoTS
Cardiological examination	New discovered systolic murmur 🖐	Cardiogenic syncope
Neurological examination	Normal	Syncope
	Extrapyramidal signs	Orthostatic hypotension
	Post-critical paralysis	Epileptic crisis

Table 1.2 Summary of the main clinical/instrumental characteristics of the subtypes of TLoC [1, 6–11]

Reflex syncope	<p>Positive history of recurrent syncope from an early age</p> <p>Triggers: prolonged orthostasis, crowded environments, pain (physical or emotional), sight of blood, urination, defecation, coughing, swallowing, etc.</p> <p>Preceded by prolonged symptoms: blurred vision, sweating, paleness, nausea, asthenia</p> <p><i>Morsus</i> (on tip of the tongue, uncommon)</p> <p>Short-lasting <i>myoclonic jerks</i> after beginning of the episode</p> <p>Urinary incontinence (possible)</p> <p>Absence of heart disease</p>
Carotid sinus hypersensitivity	<p>By stimulation of the carotid sinus (forced movements of rotation or extension of the neck)</p> <p>Short/absent prodromal symptoms</p> <p>Subjects aged >40 years</p>
Orthostatic neurogenic hypotension	<p>Predisposing factors: postprandial, postexercise period</p> <p>Prodromes: blurred vision, paleness, nausea, light headedness, pain in the neck and shoulder muscles (<i>coat-hanger pain</i>), asthenia</p> <p>(Paucisymptomatic/asymptomatic in older patients)</p> <p>Rapid recovery by lying down</p> <p>Association with supine hypertension</p> <p>Signs and symptoms of gastrointestinal and genitourinary autonomic dysfunction</p>
Iatrogenic orthostatic hypotension	<p>Diuretics, antihypertensives, antiarrhythmics, antianginals, antidepressants, antipsychotics, alpha-lytic medications</p>
Orthostatic hypotension from hypovolemia	<p>Hemorrhage</p> <p>Diarrhea and vomiting</p> <p>Dehydration</p>

<p>Cardiogenic syncope (🏠)</p>	<p>Family history of sudden death at young age During exercise or in supine position Preceded by sudden and brief palpitations Associated with chest pain and dyspnea Presence of structural cardiac abnormalities (severe aortic stenosis, atrial myxoma, cardiac tamponade) ECG findings:</p> <ul style="list-style-type: none">- Persistent sinus bradycardia <40 bpm repetitive sinoatrial blocks or sinus pauses >3 s in the awake state and in the absence of physical training- Low-frequency atrial fibrillation (<40 bpm)- Bundle branch block, intraventricular conduction disorder, ventricular hypertrophy, Q waves compatible with ischemic heart disease or cardiomyopathy- Sustained or unsustained ventricular tachycardia- Mobitz II second- and third-degree AV block malfunction of implantable device (pacemaker or ICD)- Type I Brugada pattern- ST tract elevation with type I morphology in V1–V3 leads (Brugada pattern)- Long QT (>460 ms) in repeated 12-lead ECGs- Mobitz I second-degree AV block with markedly prolonged PR interval- Paroxysmal supraventricular tachycardia or atrial fibrillation- Premature QRS complexes- Short QTc interval- Atypical Brugada patterns- Negative T waves in right precordial derivations, suggestive findings of arrhythmogenic heart disease.
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Continued

Table 1.2 Continued

Epileptic crisis	<p>Epileptic aura (ascending epigastric sensation, unpleasant smell or taste, <i>déjà vu</i> or <i>jamais vu</i>) or absence of prodromes</p> <p>Oromandibular or motor automatisms</p> <p>Head turned on one side</p> <p>Hypertonus</p> <p>Synchronous, symmetrical, prolonged limbs movements (more than 20 jerks)</p> <p>Cyanosis</p> <p><i>Morsus</i> (lingual side)</p> <p>Urinary and/or fecal incontinence</p> <p>Duration loss of consciousness approx. 1 min</p> <p>Prolonged post-critical confusion</p> <p>Stertorous breathing</p>
Psychogenic crisis	<p>Positive history of psychiatric disorders, emotional/physical trauma</p> <p>Clinical heterogeneity*</p> <p>High-frequency attacks*</p> <p>Prolonged TLoC (even 15–30 min)</p> <p>Eyes closed*</p> <p>Irregular, disorganized motor activity</p> <p><i>No morsus</i>, no trauma</p> <p>No autonomic signs (nausea, paleness, sweating)</p> <p>Absence of EEG alterations, normal blood pressure, and HR values during the episode</p>

Subclavian steal syndrome	<p>During exercise of the upper limbs</p> <p>Vertigo</p> <p>Postural instability</p> <p>Visual disturbances</p> <p>Radial hypophymia on the side of stenosis</p> <p>Hypothermia of the corresponding limb</p> <p>Different blood pressure values in the upper limbs</p>
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- Vasovagal/situational syncope: Tilt test (prolonged for 30 min)
- Pseudosyncope: Tilt test
- Differential diagnosis of convulsive syncope vs. seizure or pseudo-crisis: Tilt test with EEG monitoring
- Carotid sinus syncope/TLoC of indeterminate origin in a patient >40 year old: Tilt + carotid sinus massage

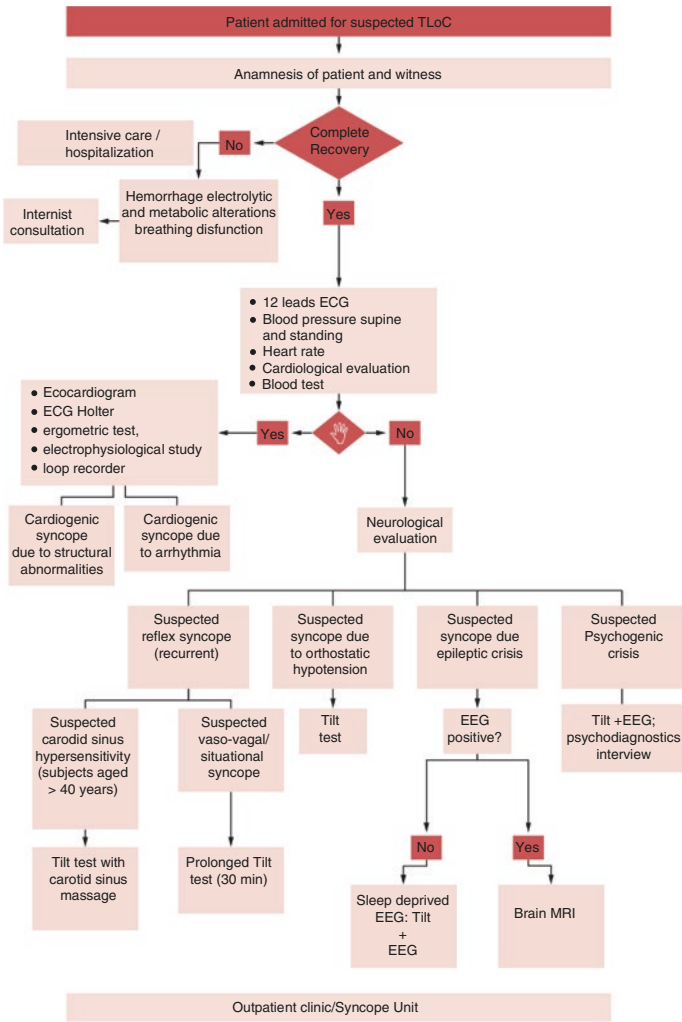
Patient Management with TLoC in the Context of Emergency [1, 12, 13]

In the context of ER, despite a careful evaluation on the basis of historical, clinical, and instrumental data, it is often not possible to reach an accurate diagnosis. Therefore, the primary objective of managing patients with TLoC is to identify “high-risk” subjects (👉) and decide which ones require intensive observation/admission.

International guidelines recommendations [1] require that a patient with even one high-risk factor remains in ER/intensive care. Conversely, the patient who does not have high-risk factors can be referred to specialists in outpatient clinics (Syncope Unit), especially if the episodes are recurrent. The patients evaluated in the ER for an episode of vasovagal/situational syncope can be reassured of the benign nature of the disorder and referred to the general practitioner.

Figure 1.2 the diagnostic/management algorithm of patients with TLoC in ER.

Figure 1.2 **Diagnostic/management algorithm of patients with TLoC in ER**



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2. Coma

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Definition

Coma is defined by the absence of arousal and of awareness lasting for more than 1 h, due to an injury or a functional interruption of the ascending reticular activating system in the midbrain and pons projecting to thalamus and cortex. Coma patients are characterized by lack of spontaneous eye opening, verbal response and voluntary movements. The motor response to a noxious stimulus, if present, is never finalistic and usually characterized by reflex motor movements. Coma must be differentiated from other alteration of consciousness such as brain death, vegetative state and delirium, although it may be difficult to do so in the emergency room (ER) [1].

The term **consciousness** indicates the presence of wakefulness and awareness in which one is able to interact with the environment [2, 3].

From a clinical point of view, consciousness consists of two distinct components:

- **Arousal (level of consciousness)** that corresponds to the state of wakefulness and presupposes the spontaneous opening of the eyes
- **Awareness (content of consciousness)** that corresponds to the ability of the patient to execute more or less complex orders

Table 2.1 shows the different types of disorders of consciousness and the main clinical aspects for differential diagnosis.

The coma patient, from a prognostic point of view, can present different evolutions within a range from brain death to good functional recovery (Fig. 2.1). Most patients exit coma within 1–2 weeks [4].

The causes that may lead to various levels of consciousness disorders can be classified as:

- **Non-structural**, usually reversible, due to severe toxic/metabolic imbalances (Table 2.2)

Table 2.1 Disorders of consciousness and mimickers [3]

State	Vigilance	Awareness	Description
Coma	Absent	Absent	No response to noxious stimuli other than reflexic, such as extensor or flexor posturing
Persistent vegetative state	Preserved	Absent	Transitioning from coma to prolonged coma, eyes may be open, especially during the day; roving eye movements; no sustained, reproducible response to stimuli; stable autonomic functions
State of minimum conscience	Present, but minimal	Present, but minimal	May make eye contact or track visual stimuli; abulic, emotionless; may mouth words or fend off pain; may hold or use an object when asked
Delirium	Altered, but not diminished or absent	Altered, but not diminished or absent	Rapidly fluctuating mental status; frequent findings include disorientation, misperception of sensory stimuli including hallucinations
Akinetic mutism	Appears intact	Absent	Lack of spontaneous motor activity
<i>Locked-in syndrome</i>	Preserved	Preserved	Complete paralysis with the exception of vertical eye movements with normal sensation and cognition
Psychogenic unresponsiveness	Preserved, but may appear altered	Preserved, but may appear altered	Changing physical examination findings; characteristic responses to the 'hand drop' test ^a or forced eye closure

^aHand drop test: one arm is raised and held in front of his face, when you let it the arm falls close to the patient's face rather than on it. Even more diagnostic is the opening of the eyes when the hairs of the nose are tickled

Figure 2.1 The potential consequences of coma [4]

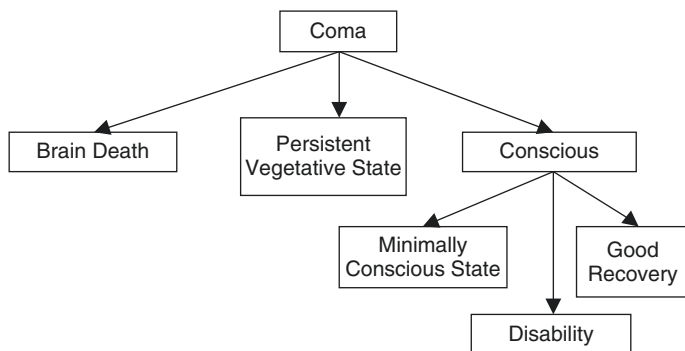


Table 2.2 Non-structural causes of coma

Metabolic	From drugs	Environmental causes/ intoxications
<ul style="list-style-type: none"> • Hypoglycaemia • Hypoxia • Hypercapnia • Hyperviscosity • Pulmonary disease • Heart failure • Diabetic ketoacidosis • Non-ketotic hyperosmolar hyperglycaemia • Hepatic encephalopathy • Uraemia • Hypo-hyponatremia • Metabolic respiratory acidosis/alkalosis • Hypo-hypercalcaemia • Myxedema—thyrotoxicosis • Parathyroid (hypo-hyper) • Adrenal dysfunction (Addison, Cushing, pheochromocytoma) • Wernicke's disease • Sepsis • Hepatorenal failure 	<p>Drugs:</p> <ul style="list-style-type: none"> • Opiates • Alcohol • Amphetamine • Cocaine—methanol <p>Drugs:</p> <ul style="list-style-type: none"> • Sedatives—barbiturate and non-barbiturate hypnotics • Narcotics • Aspirin • Acetaminophen • SSRIs, anxiolytics • Tricyclics • Anticonvulsants • Antipsychotics 	<ul style="list-style-type: none"> • Alteration of thermoregulation • Heat stroke • Hypothermia • Carbon monoxide • Ethylene glycol, bromides, paraldehyde, ammonium chloride, cyanide, organic phosphates, heavy metals • Other

- **Structural** (neurological), secondary to anatomical destruction of supratentorial or subtentorial key areas of the central nervous system (CNS) (Table 2.3)
- **Uncertain**

In the diagnostic approach to coma patients, the use of a mnemonic sequence such as **I WATCH DEATH** [5] (Fig. 2.2) can be helpful. It contains the main causes of coma; you have to remember that the most frequent causes of coma are represented by:

- Drugs/toxic substances: 40%
- Cardiac arrest: 25%

Table 2.3 Structural (neurological) causes of coma

Structural pathologies (neurosurgery)	Cranioencephalic traumas	Brain hernias
<ul style="list-style-type: none"> • Intracranial hypertension • Space-occupying lesions • Cerebral oedema • Hydrocephalus • Vasodilatation 	<ul style="list-style-type: none"> • Brain contusions • Post-traumatic intracranial bleeding • Epidural haematoma • Subdural acute and chronic haematoma • Post-traumatic SAH • Haematoma (post-traumatic intracerebral) • Hydrocephalus (obstructive, hypersecretive, aresorptive) • Brain tumours • Brain metastases • Brain abscesses • Brain haemorrhages 	<ul style="list-style-type: none"> • Cingulate (subfalcine) hernia • Central (transtentorial) hernia • Uncal hernia • Cerebello-mesencephalic hernia • Tonsillar hernia
Neurovascular	Neuroinflammations	Other causes
<ul style="list-style-type: none"> • Seizures • Non-convulsive ES • Post-ictal state • CNS infections • Meningitis • Encephalitis • Abscess 	<ul style="list-style-type: none"> • Disseminated acute encephalomyelitis • Autoimmune encephalitis • Carcinomatous meningitis 	<ul style="list-style-type: none"> • Posterior reversible encephalopathy • Osmotic demyelination syndrome • Anoxic-hypoxic encephalopathy

Figure 2.2 **I WATCH DEATH [5]**

Infectious

- Sepsis, encephalitis, meningitis, syphilis, central nervous system abscess

Withdrawal

- Alcohol, barbiturates, sedative-hypnotics

Acute metabolic

- Acidosis, electrolyte disturbance, hepatic/renal failure, other metabolic disturbances (glucose, magnesium, calcium)

Trauma

- Head, burns

CNS disease

- Hemorrhage, cerebrovascular accident, vasculitis, seizures, tumor

Hypoxia

- Acute hypoxia, chronic lung disease, hypotension

Deficiencies

- Vitamin B₁₂, hypovitaminosis, niacin, thiamine

Environmental

- Hypo/hyperthermia, endocrinopathies, diabetes, adrenal, thyroid

Acute vascular

- Hypertensive emergency, subarachnoid hemorrhage, sagittal vein thrombosis

Toxins/drugs

- Medications, street drugs, alcohols, pesticides, industrial poisons, carbonmonoxide, cyanide, solvents, etc

Heavy metals

- Lead, mercury
-

- Stroke (parenchymal haemorrhage, subarachnoid haemorrhage [SAH], pontine or cerebellar haemorrhage, extended truncal infarction): 20%
- General medical conditions: 15%

Signs and Symptoms for Differential Diagnosis

Emergency Neurological Life Support (ENLS) to complete the initial management of coma patients within first hour of arrival in the emergency department [6].

In this first hour, the suggested items to complete are:

- Stabilization of vital parameters
- Determination if coma aetiology is structural, non-structural or uncertain aetiology
- Treatment of any identified reversible causes
- Definition of diagnostic steps

Table 2.4 summarizes the items to complete in the first hour.

Identifying the cause of the coma requires a systematic approach. For the neurologist it may be helpful in the interpretation of

Table 2.4 Coma checklist for the first hour

Clinical assessment	Treatment
ABCs and C-spine <ul style="list-style-type: none">• Airway patency, circulation, breathing• Cervical spine• Venous access	<ul style="list-style-type: none">• Immobilize cervical spine if suspected cervical injury• Removing foreign body, dental prosthesis, vomiting• If GCS ≤ 8 and $PCO_2 > 45$ Torr: intubate, maintain $SaO_2 > 90\%$ and $PCO_2 < 40$ Torr
Exclude/treat <ul style="list-style-type: none">• Hypoglycaemia• Opioid overdose• Poisoning by anticholinergics	<ul style="list-style-type: none">• Hypoglycaemia: blood glucose < 70 mg/dl, 50 ml of 50% dextrose should be administered iv. Thiamine 100 mg iv should be given prior to the dextrose in patients at risk for nutritional deficiency• If opioid poisoning is suspected (history of illicit drug use, bradypnea or apnea, small pupils): naloxone 0.04–0.4 mg iv can be administered and repeated as needed in total dosing up to 4 mg• Physostigmine may be administered if anticholinergic toxicity is suspected

Continued

Table 2.4 Continued

Clinical assessment	Treatment
Evaluate if seizures or agitation	<ul style="list-style-type: none"> • Stopping epileptic seizures • Control the agitation
Monitor <ul style="list-style-type: none"> • Blood pressure • Cardiac activity • Breath frequency • SaO₂ 	<ul style="list-style-type: none"> • Treating severe arrhythmias • Keep the circle (MAP >70 mmHg)
Request <ul style="list-style-type: none"> • Serum chemistries • Arterial blood gas • Urine toxicology screen and ethanol levels if indicated • In selected cases, blood and urine culture 	
Define if the aetiology of coma is from structural or non-structural damage <ul style="list-style-type: none"> • History • General and neurological examination 	
Request urgent CT scan if suspected a structural damage or uncertain cause of coma	

clinical and neurological data to recall the main diagnostic categories and the two most common pitfalls (Table 2.5) [4].

The collection of the presenting and past medical history and the neurological examination must be rapid and focused on the distinction between coma due to structural cause and coma due to non-structural cause, distinction that is essential for planning the investigations and for a rapid therapeutic intervention [7].

History

It is vital to collect the history with the help of relatives, eyewitnesses, friends and emergency medical service (EMS) personnel.

Table 2.5 Main diagnostic categories and the two most common pitfalls in the classification of coma patients

Diagnostic categories	Two most common pitfalls
Structural injuries of one or both hemispheres	Failure to recognize <i>locked-in syndrome</i>
Intrinsic brainstem injury, or compression from surrounding damaged tissue (e.g. swollen infarcted cerebellum)	Failure to recognize psychogenic unresponsiveness
Acute metabolic or endocrine derangement (e.g. hypoglycaemia, hyponatraemia, acute panhypopituitarism)	
Diffuse physiological brain dysfunction (e.g. seizures, intoxication or poisoning, hypothermia, smoke inhalation, near drowning, heat stroke, acute catatonia, malignant neuroleptic syndrome)	

It should be investigated whether before the coma the patient presented the following disorders:

- **Epileptic seizure:**
 - Non-structural causes: hypoglycaemia, hyperglycaemia (especially non-ketotic), hyponatraemia, hypocalcaemia, hypomagnesaemia, severe liver failure, uraemia, use of drugs or substances (cocaine, amphetamines, aminophylline, lidocaine and isoniazid).
 - Structural causes: encephalitis, cerebral venous thrombosis, other structural cerebral lesions affecting the cerebral cortex or the underlying white matter, hypertensive encephalopathy (including posterior reversible encephalopathy syndrome [PRES]).
- **Delirium:**
 - Non-structural causes: metabolic or toxic encephalopathies, including encephalopathy associated with sepsis or systemic inflammatory response syndrome and body temperature disorders (hypothermia and hyperthermia).
- **Amnesia:**
 - Non-structural causes: transient metabolic disorder, such as hypoglycaemia or intoxication with alcohol or sedative drugs.

- ☐ Structural causes: seizures, especially generalized convulsive or complex partial seizures of temporal lobe origin, can also disrupt memory mechanisms for minutes to hours or more. Over two-thirds of patients with aneurysmal subarachnoid haemorrhage (SAH) experience anterograde amnesia and 17% have retrograde amnesia for time before the ictus. Psychogenic 'fugue states/twilight states' are typically associated with amnesia. Rarely amnesia can follow a vertebrobasilar ischemic attack if the thalamus is affected.
- ☒ Sphincter incontinence:
 - ☐ Suggestive of seizure.
- ☒ Visual disturbances:
 - ☐ Patients with basilar artery thrombosis may present with symptoms of the occipital lobe ischaemia (photops, vision loss). In hypertensive encephalopathy, if PRES develops, cortical blindness and seizures can occur.
- ☒ Hallucinations:
 - ☐ They can be present in patients with recreational drug use.
- ☒ Headache:
 - ☐ If associated with nuchal rigidity, it may suggest a diagnosis of meningitis or SAH. Headache of subacute onset that is intractable, worsening and is often associated with nausea and vomiting suggests cerebral venous thrombosis.
- ☒ Fever or chills:
 - ☐ CNS or systemic infection.
- ☒ History of cancer, depression, alcohol or substance abuse:
 - ☐ Cancer: structural cause.
 - ☐ Depression: drug intoxication.
 - ☐ Abuse of alcohol or substances: overdose.
- ☒ History of diabetes mellitus, adrenal, liver, kidney failure, or drug-induced or acquired immunodepression:
 - ☐ Metabolic encephalopathy, neuroinflammation.

You have to check whether the loss of consciousness has been gradual and fluctuating or fast and sudden:

- ☒ Fast and sudden: vascular damage
- ☒ Gradual and fluctuating: metabolic or infectious cause

The pharmacological history must be precise, accurate and complete. The main drug intoxications are those induced by ephedrine,

pseudoephedrine, opioids, α_2 -agonists, sedatives, antihistamines of first generation, tricyclic antidepressants and benzatropine.

The essential questions to ask to investigate the possible cause of the coma are given in Table 2.6 [4].

Table 2.6 Essential questions to ask to investigate the possible cause of coma status

Suspected cause of coma	Questions to ask
Anoxic-ischemic	<ul style="list-style-type: none"> • How the patient was found? • Where he/she was found? • Was the patient breathing when EMS arrived? • Has cardiac arrest been documented? • How long did it take before the circulation was restored? • Has there been any significant blood loss?
Toxic	<ul style="list-style-type: none"> • Which drugs/homoeopathic products did the patient have access to? • Has the patient attempted to commit suicide before? • Has the patient had a psychiatric evaluation in the past? • Has the patient had problems at work, with family, etc.? • Does the patient have problems with alcohol or drug abuse?
CNS infection	<ul style="list-style-type: none"> • Is the patient or has he/she recently been on antibiotic therapy for some infection? • Did the patient have fever or headache?
Hypo- or hyperglycaemia	<ul style="list-style-type: none"> • Is the patient diabetic or could he/she have undiagnosed diabetes? • Has the patient had episodes of diabetic ketoacidosis before? • Have there been any recent changes in antidiabetic therapy? • Could the patient have taken too much antidiabetics? • Could he/she have deliberately taken too much antidiabetics?
Hyponatraemia	<ul style="list-style-type: none"> • Could the patient have taken excess fluid? • Is the patient in diuretic therapy?
Basilar artery thrombosis	<ul style="list-style-type: none"> • Is the patient suffering from atrial fibrillation? If so, is he/she on anticoagulant therapy? Did he/she suspend it recently? • Does he/she have uncontrolled blood pressure?

General Physical Examination

None of the signs found in the physical examination are specific; however, some of them may suggest different type of intoxication or metabolic disorders.

Table 2.7 recalls the main findings of the physical examination that may help in identifying the cause of coma due to systemic disease or substance toxicity [4, 7].

Neurological Examination

In the neurological assessment of coma patients, it is essential to rapidly identify the symmetrical or focal nature of the neurological deficits (Table 2.8).

Emergency neurological examination should be rapid and focused to assess state of consciousness, cranial nerves, respiratory pattern and motor responses (Table 2.9).

State of Consciousness

The clinical scale universally used to assess impairment of consciousness is the Glasgow Coma Scale (GCS) (Table 2.10), which allows the degree of severity of coma to be quantified [8, 9].

The grade of the coma is classified according to the GCS score obtained in:

■ **Minor—GCS: 13–15**

- ☐ Torpid patient (*stupor*), obnubilated, sleepy, dormancy state, incomplete and partial order comprehension insufficient cooperation
- ☐ Slowdown in motor activity
- ☐ Slowing down thinking

Table 2.7 Findings that may suggest the presence of a systemic disease or toxicity from substances as a cause of coma

Signs or symptoms	Possible cause
Halitosis	
Dirty toilet	Uraemia
Fruity sweat	Ketoacidosis
Musty or fishy	Acute hepatic failure
Onion	Paraldehyde
Garlic	Organophosphates, insecticides, thallium
Skin	
Dry Skin	Poisoning by barbiturates or anticholinergics
Skin bullae	Poisoning from barbiturates
Profuse sweating	Cholinergic agent poisoning, serotonergic syndrome, neuroleptic malignant syndrome
Cool, pale, dry, scaly and thickened skin	Myxedematous coma
Oedema	Acute renal failure
Purple	Aspirin poisoning Meningococcal meningitis, thrombotic thrombocytopenic purpura, vasculitis, disseminated vascular coagulation
Rash	Meningitis, viral encephalitis, rickettsia
Vital parameters	
Hypotension	Overdose of antihypertensives Sepsis, fulminant meningococcal meningitis
Hypertension	Intoxication from amphetamines, cocaine and almost all party drugs
Hypothermia (<35 °C)	Alcohol poisoning, barbiturate overdose or tricyclic antidepressants Hypothyroidism, Addison's disease, hypoglycaemia
Hyperthermia (>40 °C)	Cocaine poisoning, tricyclic antidepressants, phencyclidine, salicylates Fulminant systemic infection, endocarditis, CNS infection
Cardiac arrhythmias	Tricyclic antidepressant poisoning, cocaine, glycol ethylene

Table 2.8 Identification of the site of the lesion

Neurological objectivity	Cortical	Diencephalic	Mesencephalic	Pontine-Bulbar
Eye opening	Spontaneous	To noxious stimulus or absent	Absent	Absent
Spontaneous eye motility	Erratic movements or absent	Erratic movements or absent	Absent	Absent
Eye response to movements	Conjugate deviation	Conjugate deviation	Disconjugated deviation	Absent
Pupils	Medium dilation normal reaction	Myotic normal reaction	Medium dilation fixed	Medium dilation fixed, myosis
Verbal answers	Inappropriate	Unintelligible	Absent	Absent
Spontaneous motor phenomena	Tremors, asterixis	Paratonia	None	None
Motor response to pain	Finalistic	Decorticated	Decerebrated	None
Breath	Cheyne-Stokes, yawns	Cheyne-Stokes	Neurogenic hyperpnea	Apneustic or clustered

Table 2.9 Neurological examination items in coma patient

Step of the neurological examination	Test/scale
Level of consciousness	Glasgow Coma Scale
Cranial nerves	<i>Fundus</i> OO, pupillary size and reactivity, spontaneous and reflex eye movements, oculoccephalic reflex, corneal reflexes
Breathing	Breathing pattern analysis
Motor function	Posture and spontaneous movements, motor responses to pain stimulus, presence of involuntary movements

Table 2.10 Glasgow Coma Scale

Eye opening	
Absent	1
To painful stimuli	2
To voice	3
Spontaneously	4
N/A	5
N/A	6
Verbal response (in case of intubated patient the verbal function cannot be evaluated and is indicated with Vlt)	
No sounds	1
Incomprehensible sounds	2
Inappropriate words	3
Confused, disoriented	4
Oriented, appropriate conversation	5
N/A	6
Motor response	
No movements	1
Extension to painful stimuli	2
Abnormal flexion to painful stimuli	3
Flexion/withdrawal to painful stimuli	4
Localizes painful stimuli	5
Obeys commands	6

- ☐ Absence of neurovegetative or neurological alterations
- ☐ Easy restoration of wakefulness, but if not stimulated closes the eyes and appears apathic and indifferent to the environment

■ **Moderate—GCS: 9–12**

- ☐ More pronounced loss of consciousness
- ☐ Patient does not answer questions, orders, verbal or motor stresses
- ☐ Patient reacts to painful stimuli with automatic, stereotyped, often finalist movements in an attempt to ward off the stimulus
- ☐ Signs of diencephalic impairment (abnormal pattern of breathing, e.g. Cheyne-Stokes respiration, pupil myosis and decorticated posture) may be present

This still represents a reversible stage.

■ **Severe—GCS: 3–8**

- ☐ Completely inert patient (does not react to verbal and motor orders and stresses and to painful stimuli, even intense ones)
- ☐ Abnormal pattern of breathing
- ☐ Fixed dilated pupils, dysconjugate gaze
- ☐ Decerebrate rigidity
- ☐ Mesencephalic and medullary pontine dysfunction

This represents a usually not reversible stage.

Cranial Nerves

The neurological examination of the coma patient begins with the assessment of the cranial nerves. Start by examining the pupil size and reactivity, the dilated ocular fundus and the eyeball position (Tables 2.11 and 2.12).

Pay attention to some diagnostic *pitfalls* when assessing pupils:

- Pre-existing diseases (ophthalmologic or neurological, e.g. III cranial nerve lesion) can make the pupil fixed or cause anisocoria.
- Systemic or local medications may affect pupillary function (e.g. anticholinesterases).
- If a normal pupil reaction to light is present in a patient with other signs of mesencephalic damage, one must think of a metabolic origin of the coma.
- In case of diencephalic lesions with the involvement of the descending sympathetic tract, a Bernard-Horner syndrome may occur.

Table 2.11 *Fundus OO*

Find	Cause
Vitreous haemorrhage (subialoid)	Aneurysmatic SAH (Terson's syndrome) [10] Intracerebral haemorrhage
Acute papilledema	Endocrine hypertension, hypertensive crisis

Table 2.12 Pupillary size and reactivity to light stimulus

Fixed mydriasis (>6 mm)	Unilateral	Mesencephalic lesion	Oculomotor nucleus	Uncal herniation secondary to supratentorial expansive lesion
	Bilateral	Severe mesencephalic lesion	Anticholinergic drugs	Hypoxic cerebral damage
Myosis	Unilateral	Horner syndrome	Sympathetic nerve trauma	
	Bilateral no pinpoint (1–2.5 mm)	Metabolic encephalopathies	Deep bilateral hemispheric lesions (hydrocephalus, thalamic haemorrhage)	
	Bilateral pinpoint (<1 mm)	Overdose of narcotics or barbiturates	Large pontine haemorrhage	Thalamic haemorrhage

The presence of a unilateral or bilateral gaze deviation should also be assessed. A tonic gaze deviation, usually horizontal, may suggest an ipsilateral frontal hemispheric lesion or a contralateral pontine lesion. However, differentiating a hemispheric or pontine lesion in a coma patient can be very difficult because hemiparesis is usually not detectable. In this case, the oculocephalic manoeuvre will be of help since pontomesencephalic structures responsible for the reflex are intact, and so the manoeuvre is able to overcome the conjugate eye deviation due to a cortical lesion.

A horizontal gaze deviation may also be present in the non-convulsive epileptic state disease, and it represents one of the few neurological signs that may indicate the need to perform an urgent EEG (Table 2.13) [3].

Remember that the resting eye position can be disconjugated, suggesting the following possible causes of coma:

- III cranial nerve palsy, due to a mesencephalic lesion or a transtentorial hernia.
- IV nerve palsy, generally from trauma, with upward eye deviation.

Table 2.13 Gaze position

Type	Features	Location of the damage and/or possible cause
Unilateral adduction		Medial rectus paresis due to III cranial nerve dysfunction
Unilateral abduction		Lateral rectus paresis due to VI cranial nerve lesion
Bilateral abduction		Sign of increased intracranial pressure
Oblique deviation	Vertical separation of the eye axes	Pontine or cerebellar lesion
Downwards and upwards rotation		Thalamic and upper midbrain injury (e.g. third ventricle hydrocephalus)
Horizontal conjugated deviation		Non-convulsive epileptic state Ipsilateral hemispheric stroke Contralateral pontine stroke
<i>Skew deviation</i>	Vertical strabismus	Brainstem injury

- VI nerve palsy, from intracranial hypertension or alteration of the petroclinoid ligament.
- Conjugate eye deviation in stroke can be overcome by vestibular stimulation.

The presence of wandering eye movements, *roving eye movements* and slow and random deviations similar to the ‘slow eye movements’ during sleep indicates a relative integrity of the brainstem rather than suggesting the site of the lesion.

The main changes in spontaneous eye movements and their diagnostic significance are shown in Table 2.14.

Eye and vestibular reflexes should never be assessed in a patient with trauma before excluding a cervical injury.

The oculoccephalic test (briskly but gently rotation of head from side to side or gently flexion and extension of neck) or the caloric

Table 2.14 Alterations in spontaneous eye movements and their localizing significance

Alteration	Features	Location of the lesion
Ocular bobbing	Rapid, conjugate, downward movement; slow return to primary position	Pons
Ping pong	Horizontal conjugate deviation of the eyes, alternating every few seconds	Hemisphere, vermis
Ocular dipping	Abrupt, spontaneous downward jerks of the eyes with a slow return to the midposition	Hemisphere
Periodic alternating gaze deviation	Horizontal conjugate deviation of the eyes, alternating every 1–2 min	Hemisphere, midbrain, cerebellar vermis
Convergence nystagmus	Slow eyes divergence followed by a quick convergent jerk	Midbrain
Retraction nystagmus	Eyeballs rhythmically retract into the orbit, particularly on attempting an upward gaze	Midbrain

Table 2.15 Responses to ocular-vestibular reflexes in coma patients and their localizing significance

Reflex	Response	Location of the lesion
Oculocephalic reflex (doll's eye reflex)	Eyes rotate to the <i>same side</i> to the direction of head rotation. Absence of eyes' movement	Brainstem lesion
	Eyes rotate to the <i>opposite side</i> to the direction of head rotation	Brainstem intact
Oculovestibular caloric reflex (external auditory canal irrigation with cold water)	Tonic deviation of the eyes towards the irrigated ear interrupted by very short nystagmus jerks	Supratentorial injury with intact brainstem Metabolic coma
	Unilateral or bilateral absence of response	Unilateral or bilateral brainstem injury

vestibulo-ocular test (injection of ice or cold water into the external auditory canal) assesses the integrity of the semicircular channels of the inner ear and the connection of the brainstem with the vestibular nuclei, the centres of the gaze and the nuclei of the III and VI cranial nerves (Table 2.15).

Remember, spontaneous eye movements can be compromised:

- In cerebral herniation syndromes.
- Selectively in Wernicke's encephalopathy, without pupil or other cranial nerve alterations. Impairment is secondary to selective damage to the structures of the grey matter adjacent to the ventricles and the cerebral aqueduct including the vestibular nuclei involved in the VOR.
- After taking high doses or accumulating sedative medications. Ocular-vestibular reflexes in this case can be selectively and transiently abolished.

The integrity of the corneal reflex (closing of the eyelid and upward deviation of the eye, Bell phenomenon, following corneal

Table 2.16 Corneal reflex and site of injury

Corneal Reflex	Location of the lesion
No response	Inferior pons
Disappearance of Bell’s phenomenon	Above middle pons (V cranial nerve nucleus)
Presence of Bell’s phenomenon, disappearance of the closure of the eyelids	Nerves and nuclei of VII cranial nerve

stimulation) is a marker of proper operation of the tegmental pathways of the brain stem from the midbrain to the lower pons (Table 2.16).

To evaluate motor responses in coma patients, it is necessary to evoke them by applying a painful stimulus by compressing the supraorbital nerve, the temporomandibular joint or the nail bed.

The absence of a response or a response in decerebration or decortication has little localizing and prognostic significance, as they can be present both for focal lesions and for diffuse damage of the CNS. It should be remembered that often responses in decerebration and decortication might be present in the same patient. It is possible, however, by carefully observing the patient at rest and after painful stimulation, to acquire some information that will help us to identify the site of the injury and the cause of coma (Table 2.17).

Epileptic seizures are more commonly myoclonic (with synchronous bilateral contractions, distinct from multifocal myoclonus) and may be present in a number of metabolic encephalopathies, including hyponatraemia, hyperosmolar states (especially in non-chaetotic hyperglycaemia, in which convulsions can be misleading because they are focal), hypocalcaemia, extreme hypercalcaemia, uraemia, advanced hepatic encephalopathy, hypoglycaemia and hypoxic-anoxic encephalopathy after cardiac arrest. In this last situation, the myoclonic epileptic state is usually fatal, with no recovery of consciousness.

Table 2.18 shows the most frequent involuntary movements observed in coma patients.

Table 2.17 Useful information to identify the site of the injury and the cause

If	Think about
Unnatural attitudes of the limbs	Fractures or paralysis
Head rotation on one side and contralateral hemiparesis	Supratentorial lesion
Head rotation on one side and ipsilateral hemiparesis	Brainstem injury
Extensor hypertonus of the four limbs and internal rotation of the shoulders (posture of decerebration)	Bilateral midbrain and pons injuries Coma from metabolic causes Bilateral supratentorial lesions with involvement of the motor pathways It's an unfavourable prognostic sign
Arms adducted, flexed at the elbow and wrist, with the legs extended and feet plantar flexed (decorticated rigidity)	Higher lesion with poor localizing capacity Less severe prognostic sign of decerebration because it may be reversible If unilateral, it is less severe and may indicate lesions of the entire pyramid system from the cortex to the brainstem

Table 2.18 Involuntary movements in coma patients

Type	Cause
Stereotyped tonic-clonic motor phenomena	Epileptic seizures
Generalized myotonic jerks	Hypoxic-anoxic encephalopathy Lithium, cephalosporins or pesticides intoxication
Diffuse or localized arrhythmic movements (<i>flapping</i>)	Metabolic coma
Rhythmic myoclonus	Brainstem damage
Tetany	Hypocalcaemia
Cerebellar tonic fits	Intermittent herniations of cerebellar tonsils

Brain Herniation Syndromes

Site	Features
Subfalcine	Progressive deterioration of consciousness with or without hemiparesis, and late III cranial nerve palsy
Uncal	Early paralysis of the motor system before the impairment of consciousness
Central (diencephalic)	Begins with myotic pupils followed by consciousness impairment, with irreversible late oculomotor paralysis
Rostrocaudal	Abrupt loss of consciousness with paralysis of the cranial nerves
Tonsillar	Respiratory arrest followed by hypertension, then hypotension, coma and often brain death

Oculomotor signs associated with the herniation include:

- Initial tendency to deviation or conjugated deviation of gaze to one side.
- Subsequently pupillary asymmetry secondary to stretching of the third cranial nerve (oculomotor) over the ipsilateral *clivus* to brain damage. Pupillary asymmetry is characterized by dilation of the pupil ipsilateral to the lesion (present in about 20% of cases).
- Loss of pupillary reactivity and paralysis of extraocular muscles.
- In the following stages, the contralateral pupil loses its reactivity due to the intrinsic damage of the midbrain.

Diagnostic Procedures

Arterial Blood Gas Analysis

It should be performed in all coma patients.

- Normal: pseudo-crisis, catalepsy.
- Hyperventilation with metabolic acidosis: possible causes include uraemia, diabetic ketoacidosis, lactic acidosis or salicylate poisoning, methanol or ethylene glycol intoxication.

- Hyperventilation with respiratory alkalosis: possible causes include liver failure, acute sepsis, and any cardiopulmonary condition that causes hypoxaemia, acute phase of salicylate poisoning or psychogenic hyperventilation.
- Hypoventilation with respiratory acidosis: coma occurs only in the presence of severe hypercapnia. The possible causes are respiratory failure secondary to pathology of the central or peripheral nervous system, thoracic disorders.
- Hypoventilation with metabolic alkalosis: consciousness is usually not compromised. Causes include vomiting and alkalis ingestion. If the patient is unconscious, suspect a psychogenic or other cause of altered consciousness.

Serum Chemistries

Always required: blood sugar, plasma electrolytes (calcium, sodium, potassium, magnesium and phosphate), urea and creatinine.

Additional laboratory tests may be performed depending on suspected diagnosis (Table 2.19):

- Liver function test if liver failure is suspected. Remember that INR is sensitive to acute liver failure.
- Toxicology screen. It cannot be exhaustive. In the absence of accurate information and with suspicion of toxic coma think of alcohol, benzodiazepines, barbiturates, opiates, cocaine, amphetamines, tricyclic antidepressants, salicylates, paracetamol and other agents.

Table 2.19 Laboratory values compatible with coma in patients with metabolic changes

Parameter	Serum level
Hyponatraemia	<100 mmol/l
Hypernatraemia	>160 mmol/l
Hypercalcaemia	>3.4 mmol/l
Hypercapnia	>9 kPa
Hypoglycaemia	<40 mg/dl
Hyperglycaemia	>900 mg/dl

- Blood culture if fever or hypothermia.
- Plasma levels of carboxyhaemoglobin if carbon monoxide poisoning is suspected. Remember that smokers may have slightly elevated levels.
- Pyruvate, erythrocytic transketolase, serum thiamine if suspicion of Wernicke's encephalopathy.
- Specific pharmacological or metabolic examinations may be identified and performed based on medical history and clinical picture.

The *anion gap* and the *osmolar gap* must always be calculated (Table 2.20).

Neuroimages

Performing neuroimaging (CT or MRI) is essential in the diagnostic path of the coma patient.

Usually in the emergency room the most easily available diagnostic method is the CT scan. Table 2.21 shows the most frequent alterations that can be detected on neuroimaging in coma patients, depending on the neuroradiological method used (3).

CSF Examination

It should be performed on all coma patients with negative neuroimages and no other identified causes of coma.

Table 2.20 Gaps and their interpretation

GAP	Interpretation
Anion gap = $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$	Normal value: 11–13 mEq/l may increase during metabolic acidosis or intoxication by methanol, ethanol, paraldehyde or salicylates
Osmolar gap = $2 (\text{Na}^+ + \text{K}^+) + \text{glucose}/18 + \text{urea nitrogen}/2.8$	Normal value: <10 mosmol/l may increase during intoxication by methanol, ethylene, glycol (antifreeze), isopropyl glycol

Table 2.21 Frequently occurring changes in neuroimaging in coma patients

Alteration	Possible cause
Brain CT scan	
Expansive lesion	Haematoma, haemorrhagic contusion, stroke in the territory of the middle cerebral artery
Haemorrhage in cranial base cisterns	SAH from aneurysm rupture, cocaine abuse
Multiple haemorrhagic infarctions	Cerebral venous thrombosis
Intraventricular haemorrhage	Endocarditis, coagulopathies, vasculitis, thrombotic thrombocytopenic purpura
Diffused cerebral oedema	Cardiac arrest, fulminant meningitis, acute liver necrosis, encephalitis
Acute hydrocephalus	Obstruction of the aqueduct, colloid cysts, cancer of the pineal region
Cerebellar or pontine haemorrhage	Hypertension, arteriovenous malformation, cavernous angioma
Trauma in the white matter	Head trauma
Brain MRI	
Bilateral lesion of caudate and putamen	Poisoning by carbon monoxide, methanol
Hyperintense signal along the sagittal, rectal or transverse venous sinus	Cerebral venous thrombosis
Corpus callosum, white matter injury	Severe head injury
Confluent lesions, diffuse hyperintensity in the white matter and in the basal ganglia	Acute disseminated encephalomyelitis, PRES, immunosuppressive or chemotherapeutic toxicity, metabolic leukodystrophy
Pontine lesion with the shape of a trident	Central pontine myelinolysis
Thalamic, occipital and brainstem lesions	Basilar artery acute thrombosis
Hyperintensity of the temporal and frontal lobes	Encephalitis from herpes simplex

The lumbar puncture must provide:

- CSF open pressure
- Description of the appearance of CSF
- Analysis of protein, cells and glucose
- CSF culture, China ink staining and cryptococcal antigen research
- Titration of viral load and PCR in CSF

Electroencephalogram

It is advisable to request this urgently even in ER when the cause of the coma is not clear and the reflexes of the brainstem are preserved.

At least 14% of patients who did not wake up after a seizure have a non-convulsive epileptic state.

EEG is also useful for diagnosing pseudo-crisis or psychogenic seizures, in suspected acute herpes simplex encephalitis (sensitive in >80% of cases), hypothermia, hyperthermia, SAH and sepsis.

Electromyography

It can help rule out a neuromuscular cause:

- Neuromuscular block secondary to a prolonged action of muscle relaxants.
- Acute polyneuropathy: inflammatory demyelinating polyneuropathy and the axonal form of Guillain-Barré syndrome, etc.

Therapeutic Approach

The initial treatment of the coma patient should include the rapid correction of vital parameters and laboratory tests, which are usually responsibility of the emergency physician and/or the resuscitator.

The empirical therapy of the coma patient, often abbreviated to 'DONT', consists of:

- Dextrose iv
- Oxygen

- Naloxone iv
- Thiamine iv

Oxygen therapy should be initiated to immediately correct possible hypoxia-induced coma.

Dextrose is indicated in the suspicion of hypoglycaemic coma even if the blood glucose value is not available.

Thiamine is commonly administered together with dextrose to avoid Wernicke's encephalopathy in predisposed patients.

Naloxone rapidly antagonizes coma and respiratory depression in narcotics overdose but, because of its short half-life, multiple doses may be needed.

Flumazenil specifically antagonizes benzodiazepines but is not routinely administered empirically as it can precipitate a convulsive epileptic state. It may be indicated in iatrogenic coma secondary to benzodiazepine intoxication [6].

Table 2.22 shows the main procedures for the stabilization of the patient.

Once the patient is stabilized, therapeutic interventions will depend on the cause of the coma. Table 2.23 shows the therapeutic priorities in case of structural coma or CNS infection [3, 11].

Table 2.22 Therapeutic interventions for the stabilization of comatose patients

Parameter	Treatment
Oxygen saturation $\leq 95\%$	SaO ₂ with 40% face mask
Intubate if	Unprotected airways
	Irregular and ineffective respiratory drive with poor oxygenation
	Major facial trauma

Table 2.22 Continued

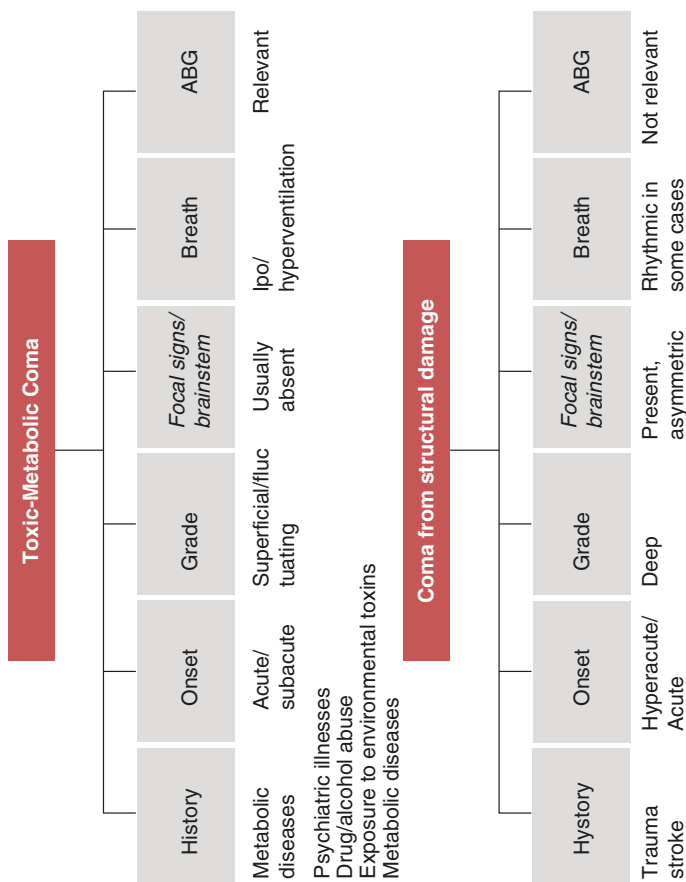
Parameter	Treatment
Hypotension	Trendelenburg Saline solution 500–1000 ml in rapid infusion, then 150 ml/h. If no answer: phenylephrine bolus iv 100 µg
Hypertension (MAP >130 mmHg)	Labetalol 10 mg iv
Hypothermia	Heated blankets
Hyperthermia	Refrigerated blankets, ice bag, sponges with ice water
Certain or suspected hypoglycaemia	Glucose 50% 50 ml + thiamine 100 mg iv
Suspected opioid poisoning	Naloxone 0.4–2 mg iv every 3 min
Suspected benzodiazepine poisoning	Flumazenil 0.2 mg/min iv slowly (max 5 mg). Contraindicated in the epileptic patient, in the suspicion of epileptic seizures or of intoxication by tricyclic antidepressants
Hypercalcaemia	Rehydration with saline solution followed by parenteral administration of bisphosphonates
Severe hyponatraemia	3% hypertonic saline solution and furosemide via central venous catheter
Toxic coma	Always evaluate haemodialysis or hemoperfusion

Table 2.23 Therapeutic priorities in patients with an acute structural coma

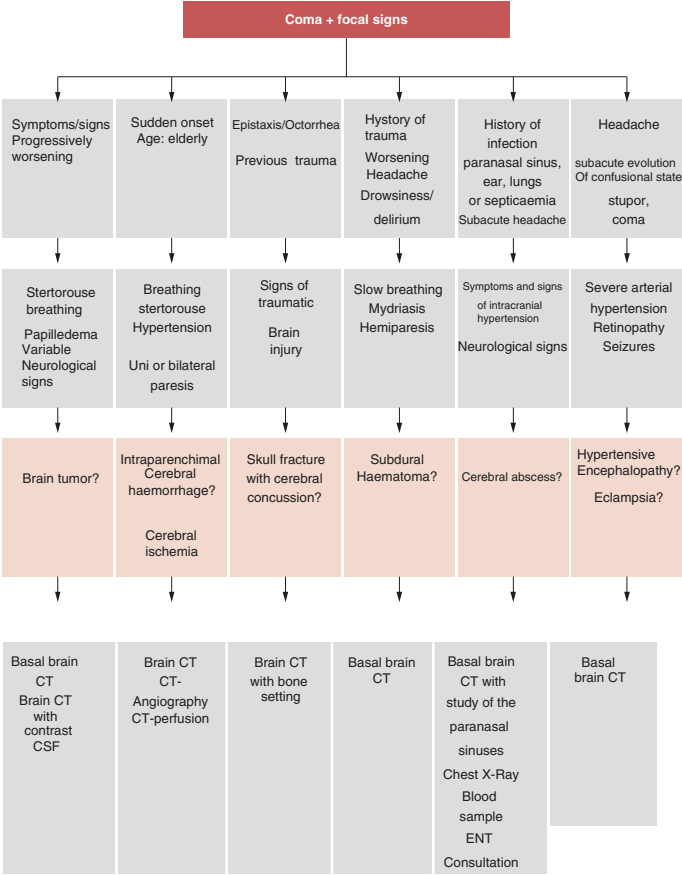
Structural cause	Treatment
Hydrocephalus	Ventriculostomy
Mass occupying space	Consider mass evacuation to reduce intracranial pressure. If mass cannot be removed consider decompressive craniectomy
Intracranial hypertension	Consider administration of mannitol 1–2 g/kg, repeatable every 30–40 min
Infectious cause	
CNS infection	Cefotaxime 2 g iv every 6 h, Vancomycin 20 mg/kg iv every 12 h, Ampicillin 3 g iv every four hours Aciclovir 10 mg/kg every 8 h Consider administration of dexamethasone 0.6 mg/kg daily before administration of antibiotics to be continued for 4 days

Appendix

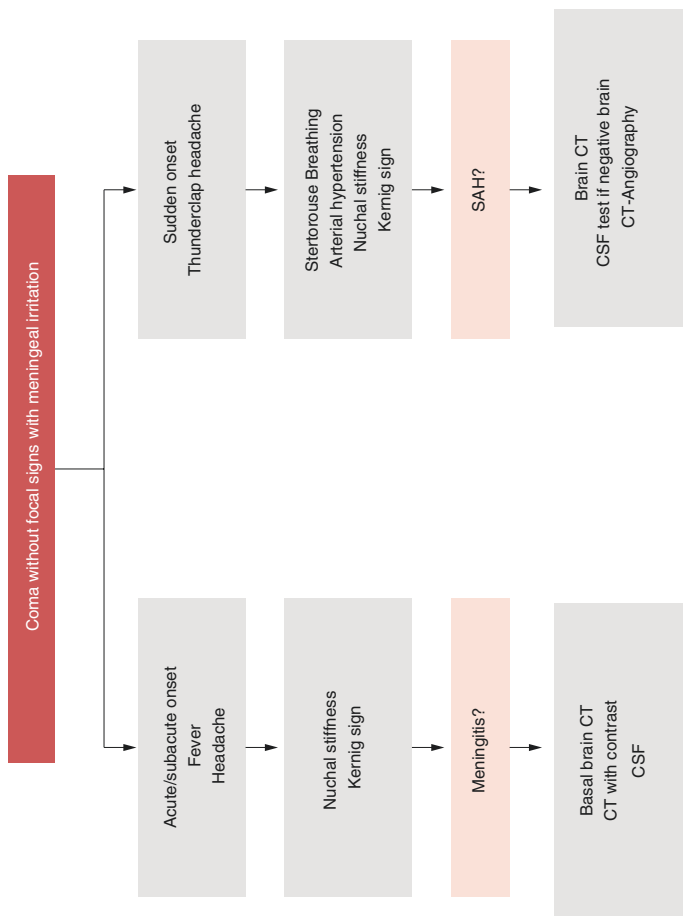
Algorithm 2.1



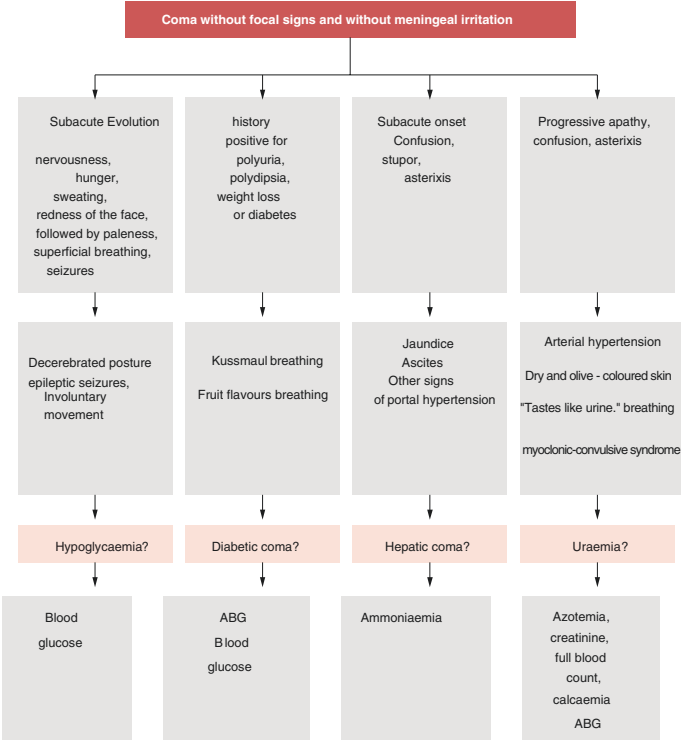
Algorithm 2.2



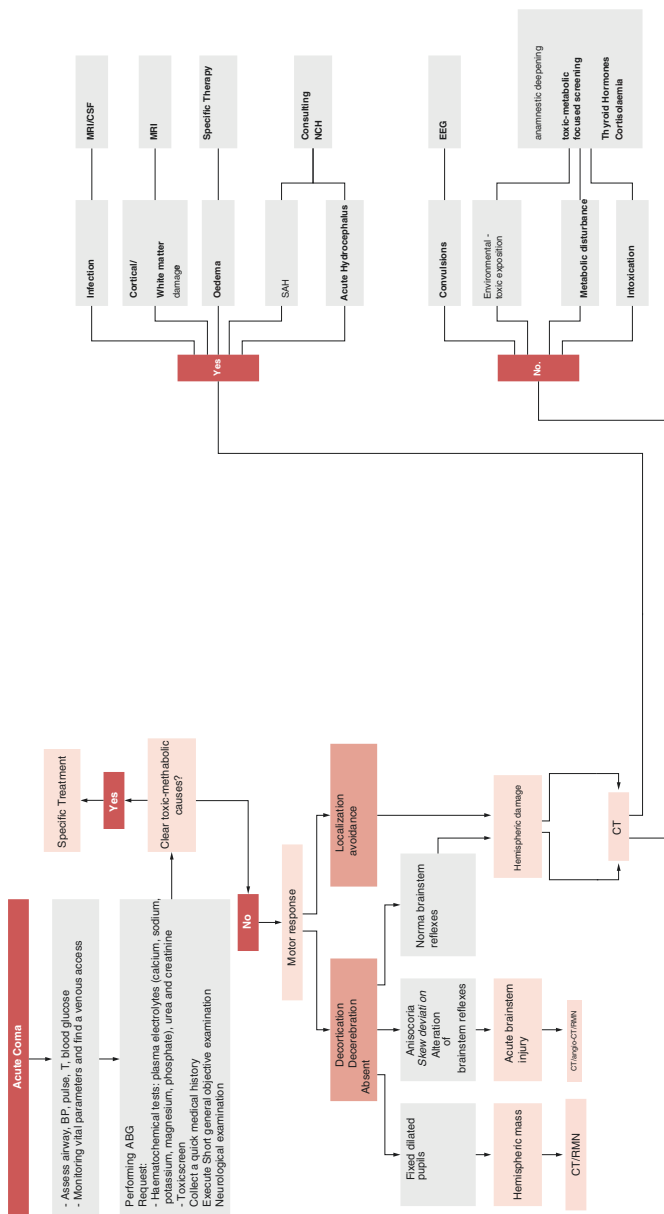
Algorithm 2.3



Algorithm 2.4



Algorithm 2.5



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3.

Delirium/Acute Confusional State

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Definition

Delirium is a common cause of disturbed behavior in medically ill people and is often undetected and poorly managed. It is a condition at the interface of medicine and psychiatry that is all too often owned by neither [1]

Delirium is classically defined as an acute, transient, global, organic disturbance of cognitive functions that leads to loss of attention and fluctuating impairment of consciousness.

Delirium is a specific (and common) condition of acute confusional state well defined by the DSM V and in the literature. It is mainly (but not exclusively) found in elderly people with multiple pathologies and often has a multifactorial origin but is typically triggered by a general medical condition.

Delirium more often occurs during hospitalization or is the cause of admission to hospital. In the Emergency Room (ER), confusional state is most frequently observed due to the effect (intoxication or withdrawal) of substances or drugs, metabolic imbalances or underlying medical diseases, or is due to specific neurological disorders, such as the clinical onset of encephalitis, including limbic encephalitis, stroke for some localizations, or head trauma. Even the patient with a nonconvulsive epileptic status can reach ER with a confusional state, before that epilepsy was diagnosed (for this condition, refer to Chap. 4).

The onset of delirium in hospitalized patients (in-hospital delirium, defined as incident delirium) is burdened by increased mortality, is associated with a lengthening of hospital stay, may speed the evolution toward dementia, and increases the need for transfer to protected facilities (institutionalization). Moreover, it has a higher rate of complications for excessive immobility that can promote urinary or pulmonary infections, venous thrombosis, pulmonary embolism, and sepsis, while psychomotor agitation and wandering predispose to falls and fractures.

Furthermore, according to several studies, from 32% to 67% cases of delirium are not correctly recognized. The missed diagnosis is

associated with a high risk of morbidity and mortality both because the associated organic cause is not recognized and because the associated behavioral disorder is not treated [2, 3]. Synonyms of delirium: **acute confusional state**, acute organic cerebral syndrome (reaction to), metabolic encephalopathy, exogenous toxic psychosis, and sundown syndrome.

Diagnostic Criteria for Delirium According to DSM-V

- A. **Attention disorder** (i.e., reduced ability to direct, focus, sustain, and shift attention) **and awareness** (reduced orientation to the environment).
- B. The disturbance develops over a **relatively short** period of time (usually hours to a few days), represents a change from baseline attention and awareness, and **tends to fluctuate in severity throughout the** course of the day.
- C. There is an additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
- D. Disturbances in criteria A and C **cannot be explained by another preexisting** (established or evolving) **neurocognitive disorder** and do not occur in a context of a severely reduced level of arousal (e.g., coma).
- E. There is evidence from the history, physical examination, or laboratory findings that delirium is a **direct consequence** of another medical condition, intoxication, or withdrawal of drugs, exposure to toxins, or is due to multiple etiologies.

Classification

The DSM-V distinguishes the delirium by **duration** in:

- **Acute:** lasting a few hours or days
- **Persistent:** lasting weeks or months

The following clinical forms are distinguished according to the behavior and **reactivity of the patient:**

- **“Hyperactive” form** (22%). The patient is alert, hyperactive, with excessive reaction to stimuli.

- **“Hypoactive” form** (26%). The patient shows lethargy, with reduced psychomotor activity (the “hypoactive” form of delirium is more common in older people, is often not recognized, and is associated with a greater frequency of complications and mortality) [4–6].
- **“Mixed” form** (42%). Alternating hyper- and hypoactive forms during the day or during the episode.
- **“Non-classifiable” form** (10%). No psychomotor disorders.

Regarding the **severity of the clinical picture**, we distinguish three levels:

- **Mild:** The disturbance can go unnoticed and only occasional inconsistent observations and the inability to recall the events of the previous hours reveal its presence; relatively preserved spatial/temporal orientation.
- **Moderate:** Ability to talk for short moments but slow and inconsistent thinking; inability to persist on the same subject and to provide appropriate responses; spatial/temporal disorientation; easy distractibility; inability to recall what happened in the previous hours; possible alternation of irritability/agitation and hypoactivity/lethargy.
- **Severe:** Inability to do more than execute the simplest orders; lack of awareness of what is happening, often inability to recognize people and objects; conceptual processes: few or all missing; language: few words, without a logical content; attentional deficit often masked by the delusional hallucinatory state.

The DSM-V distinguishes the following subtypes according to their **etiology**:

- **Intoxication of substances** delirium, e.g., alcohol, opioids, hypnotics, amphetamine, and other substances.
- **Substance withdrawal** delirium, e.g., alcohol, opioids, sedatives, hypnotics, and anxiolytics.
- **Medication-induced** delirium. This definition applies when symptoms in criteria A and C (DSM-V) occur as a *side effect* of a prescribed drug.
- Delirium due to **other medical condition**. When there is evidence from history, objective examination, laboratory findings that the disorder is a consequence of *one* underlying medical condition.

- Delirium from **multiple etiology**. When there is evidence from history, objective examination, and laboratory findings that the disorder has *more than one* cause (more than one medical disorder, or a medical condition plus substance intoxication or medication side effect).

Epidemiology and Pathophysiology

Acute confusion state is a common symptom in the hospital. It is estimated that 10–20% of the over 65 or older patients who are admitted to hospital present delirium as a symptom (defined as prevalent delirium), while 10–30% of the hospitalized elderly show delirium during their stay (defined as incident delirium) [2, 3, 7].

The hospitalized aged patients develop delirium in different percentages depending on the context of care: medical departments (10–25%), surgical departments (7–52%), hip fractures (20–30%), stroke (13–50%), and coronary surgery (23–34%). In intensive care units, delirium occurs more frequently: 40% at all ages and 70% in the elderly. In nursing homes, the percentage in the elderly rises to 70% [3].

Regarding pathogenesis, the neurotransmitters that may play a role in delirium include acetylcholine, dopamine, serotonin, nor-adrenaline, glutamate, and GABA. In the pathophysiology of delirium, several factors interact with each other. Hypoxemia, fever, dehydration, and metabolic changes lead to an overall impairment of brain metabolism, which, in turn, leads to a reduced synthesis, and release of neurotransmitters. Systemic inflammatory states (because of trauma, surgery, or infection) cause microglia activation and increased levels of cerebral cytokines. Both conditions, as well as, by direct action, the drugs, can cause an imbalance in the neurotransmitters and an alteration in synaptic communication [8].

Delirium is more frequent in the elderly, in particular in the frail elderly due to multiple comorbidities, and in people with dementia or with previous or concomitant neurological disorders. In this context, the concepts of vulnerability and of “cognitive reserve” should be introduced, according to which a precipitating factor

(see below), even a minor one can induce delirium in a patient with reduced cognitive reserve (predisposing factor) [3].

Prognosis

Delirium in hospitalized patients is associated with higher mortality [9, 10] compared to hospitalized patients without delirium (8% vs 1%), length of the hospital stay (12 days vs 7 days), and increased need for institutionalization (16% vs 3%). Furthermore, the occurrence of delirium is associated with an increased mortality at 12 months (HR 3.44 CI 2.05–5.75 vs 2.11 CI 1.18–3.77) [11, 12], and at 5 years, the clinical outcome in nondemented patients with delirium is superimposable on the clinical outcome in patients with severe dementia.

These data are confirmed by a recent cohort study [13] according to which in patients 65 years of age or older who were evaluated: patients with delirium were at higher risk of death (raw mortality OR [CI 95%]: 5.46, $p < 0.001$), stay significantly longer in intensive care unit (crude HR for discharge: 0.40, $p < 0.001$) and in the hospital (crude HR for discharge: 0.25, $p < 0.001$), needed more hours of care (average nursing hours plus 64.8, $p < 0.001$), and generated significantly higher costs per case (average crude cost difference [in thousands CHF]: 20.9 < 0.001).

Rating Scales

In addition to the **MMSE** (*Mini Mental State Evaluation*) [14], a widely used test, easy and quick to administer and with good sensitivity, to allow better delirium identification several scales have been worked out:

- **CAM** (*Confusion Assessment Method*). It is the most widely used diagnostic tool that the authors recommend for delirium detection; it consists of four items based on the diagnostic criteria of the DSM-III-R for delirium, requiring (1) the presence of acute onset and/or fluctuating course; (2) attention deficit; (3) disorganized thinking; and/or (4) alertness impairment. The specificity and sensitivity of the test are high (Table 3.1) [6, 15].

Table 3.1 The Confusion Assessment Method (CAM) *diagnostic algorithm*

1. Acute onset and fluctuating trend 0 = no; 1 = yes	This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
2. Inattention 0 = no; 1 = yes	This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
3. Disorganized thinking 0 = no; 1 = yes	This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
4. Altered level of consciousness 0 = alert; 1 = hyperalert, lethargic, drowsiness, stupor, coma	This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium requires the presence of 1, 2, and, alternatively, 3 or 4

Modified by Inouye et al. [3]

- **CAM-ICU** (*Confusion Assessment Method-Intensive Care Unit*). This is a version of CAM designed for patients unable to verbally communicate, especially when intubated in intensive care. It allows the assessment of attention deficit by auditory or visual tests that require behavioral responses (e.g., shaking hands), and of disorganization of thinking through yes/no logic questions. CAM-ICU can only be administered if the patient can be awakened in response to a voice command without the need for physical stimulation [16, 17].
- **4AT**. Compared to CAM, it does not require specific training, and it displays a shorter execution time. Includes the evaluation of 4

items: alertness (score 0–4), orientation (score 0–2), attention (score 0–2), and acute change/floating course (score 0–4). A final score ≥ 4 has shown good sensitivity and specificity for the diagnosis of delirium. It can be used in a large variety of clinical settings and it doesn't require prior training (Table 3.2) [18, 19].

Table 3.2 4AT

Item	Score
Alertness This includes patients who may be markedly drowsy (e.g., difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.	
<ul style="list-style-type: none"> • Completely attentive, not agitated throughout the evaluation • Moderate drowsiness for less than 10 s after waking up, then normal • Clearly abnormal level of attention 	0 0 4
Orientation Ask the patient about age, date of birth, place (name of the hospital or building), and current year	
<ul style="list-style-type: none"> • No mistakes • 1 mistake • 2 or more mistakes/untestable 	0 1 2
Attention Ask the patient: "Please tell me the months of the year in backwards order, starting at December." To assist initial understanding one prompt of "What is the month before December?" is permitted.	
<ul style="list-style-type: none"> • Achieves 7 months or more correctly • Starts but scores <7 months/refuses to start • Untestable (cannot start because unwell, drowsy, inattentive) 	0 1 2
Acute change or fluctuating course Evidence of significant change or fluctuation in: alertness, cognition, and other mental function (e.g., paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24 h	
<ul style="list-style-type: none"> • No • Yes 	0 4

Score:

4 or above: possible delirium \pm cognitive impairment

1–3: possible cognitive impairment

0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

- **DSI** (*Delirium Symptom Interview*). It is a structured interview. Detects the presence or absence of seven DSM-III criteria for delirium. Delirium is present if disorientation; perceptual disturbances or disturbances of consciousness have appeared in the previous 24 h [20].
- **NeeCHAM Confusion Scales**. Nine items divided into three sections: section (1) “information processing” (score 0–14 points) assesses the components of cognitive status; section (2) “behavior” (score 0–10 points) assesses observed behavior and performance ability; section (3) “performance” (score range 0–16 points) assesses vital function (i.e., vital signs, oxygen saturation level and urinary incontinence pathway). The total score may vary from 0 (minimum function) to 30 (normal function). Delirium is present if the score is ≤ 24 points [21].
- **iCDsC** (*Intensive Care Delirium screening Checklist*). Screening tool for delirium at the bedside of the patient, useful in intensive care units; checklist of eight elements based on DSM-IV criteria; items are marked as 1 (present) or 0 (absent), a score ≥ 4 points indicates delirium [22].
- **Cognitive Tests for Delirium**. It can be used in patients unable to speak or write. Evaluates orientation, attention, memory, understanding, and vigilance, primarily in the visual and auditory modes. Each individual domain is rated with a score from 0 to 6 in two point increments, except for understanding, which has unitary increments. Total scores range from 0 to 30, with the highest scores indicating better cognitive function [23, 24].

Some scales also measure the **severity of** the delirium:

- **DRS-R98** (*Delirium Rating Scale*). It consists of a scale with 16 items, including 13 severity items and 3 diagnostic items. The severity score varies from 0 to 39. For the diagnosis of delirium, the score is ≥ 15 points, a higher score indicates greater severity of the delirium [25].
- **MDA** (*Memorial Delirium Assessment scale*). Measures the severity of the delirium on a scale of 10 items, points for each item from 0 to 3 based on observation, the test score varies from 0 to 30 [26].
- **CAM-Severity Scale** (*CAM-S*). Based on both the short and long versions of CAM, it has strong psychometric properties and high

predictive validity for important clinical outcomes related to delirium, including length of stay, hospital costs, placement in a nursing home and mortality [27].

For a more accurate and standardized definition and detection of delirium, the authors recommend performing the clinical assessment according to the CAM scale, assuming it is possible to train operators in the correct use of the instrument. Where no specific training is possible, the clinical assessment can be performed using the 4AT scale.

Identification of Predisposing and Precipitating Factors

Since many cases of delirium have multifactorial genesis, it may be useful to categorize the risk factors into predisposing factors (pre-existing characteristics of the patient, vulnerability) and precipitating factors (pathogenic insults that occur at the time of hospitalization). Patients with high vulnerability (e.g., dementia, severe comorbidity) may also experience delirium due to relatively minor precipitant factors (intake of a dose of benzodiazepines, positioning of bladder catheters) (Tables 3.3, 3.4, 3.5).

The predisposing factors most frequently indicated in the literature are (from most important to minor) advanced age, preexisting dementia, severe concomitant medical conditions, concomitant intake of multiple drugs, alcohol abuse, hyponatremia, depression, pain, auditory and visual impairment.

Table 3.3 Predisposing factors

-
- Elderly
 - Cognitive impairment (25% delirium in dementia, delirium in 40% dementia in hospital)
 - Chronic polypathology
 - High number of drugs
 - Sensory deficits
 - Psychoactive drugs
 - Alcoholism
 - Pain
-

Table 3.4 Neurological causes of delirium

Cerebrovascular diseases
Hemorrhagic stroke, ischemic stroke, subarachnoid hemorrhage, vasculitis
Migraine
Confusional migraine (migraine that alters the consciousness state)
Inflammation or infection
Acute demyelinating encephalomyelitis, cerebral abscess, central nervous system vasculitis, encephalitis, meningitis, meningoencephalitis
Epilepsy
Nonconvulsive epileptic state, postictal state
Trauma
Subdural hematoma, traumatic brain injury
Cancer
Meningeal carcinomatosis, primary, or metastatic brain tumors

Mnemonics have been developed to recall the main precipitating factors of delirium [28]:

- **Vindicate:** Vascular; Infections; Nutrition; Drugs; Injury; Cardiac; Autoimmune; Tumors; Endocrine.
- **Delirium:** Drugs; Eyes/ears; Low oxygen; Ischemia; Retention; Infections; Underhydration; Metabolic disorders; Sleep deprivation; Subdural.

Delirium is more frequent in stroke patients (13%) than in other acute patients, such as those with acute coronary heart disease. In stroke patients delirium does not qualify as a nonspecific consequence of acute disease or hospitalization but is caused by hemispheric brain damage and metabolic changes [29]. Stroke unit patients compared to stroke patients hospitalized in general wards have a lower incidence of delirium [30]. This symptom manifests itself more in association with preexisting dementia (OR 18.1), hemianopsia (OR 12.3), apraxia (OR 11.0), advanced age (OR 5.5), infections (urinary or pulmonary tract, OR 4.9).

A systematic review [31] showed that in patients with delirium hospital mortality (OR 4.71) is higher at the early stages of stroke

Table 3.5 Precipitating factors**Metabolic disorders and medical diseases**

Hepatic encephalopathy
Uremia
Hypoglycemia
Hypoxia
Hydroelectrolytic disorders (hypo-/hypernatremia, hyper-/hypoosmolarity, hypo-/hypermagnesemia)
Acute heart failure
Acute infections (respiratory, urinary, sepsis)
Acidosis
Malnutrition
Porphyria
AIDS

Toxic and industrial exposures

Carbon monoxide
Organic solvents
Lead
Manganese
Mercury
Carbon disulfide
Heavy metals

Vitamin deficiency

Thiamine
B12
Niacin
Folic acid

Endocrinopathies

Thyroid
Parathyroid
Pituitary
Adrenal

Drugs

Alcohol
Caffeine
Hallucinogens
Amphetamines
Meperidine, other narcotics

Invasive

Bladder catheter
Venous lines

Table 3.5 Continued

Physical restraint tools	
Abstinence syndrome	
Alcohol	
Benzodiazepines	
Neuroleptics	
Depression	
Drugs	
Psychotropic	Phenothiazines Clozapine Lithium Tricyclic antidepressants Trazodone Anticonvulsants Phenobarbital Phenytoin Valproate Carbamazepine
Other CNS drugs	Antiparkinsonian drugs Sedative-hypnotic drugs Anticholinergic Antihistaminic Cimetidine Disulfiram Ergot alkaloids Methyl dopa
Cardiovascular agents	Beta-blockers Clonidine Digoxin
Anti-infective drugs	Acyclovir Amphotericin B Cephalixin Chloroquine Isoniazid Rifampicin
Cytotoxic drugs	
Anti-inflammatory drugs	Salicylate Steroids
Surgical interventions	
Trauma	
Hip fracture	

and at a 12-month interval (OR 4.91) compared to patients without delirium. Delirium led to a lengthening of hospital stay by more than 9 days and the discharge not at home (OR 3.39).

Differential Diagnosis

History

As far as possible, patient's history should be checked with family members or acquaintances.

The Most Important Questions

- What is the patient's age?
- Who does he live with?
- Is it possible to collect anamnestic data?
- What is the patient's usual cognitive level?
- What are the patient's health problems?
- What medications does the patient take?
- Is the patient abusing alcohol or other drugs? Did he recently stop a substance he was dependent on?
- Has the patient had any recent fever, infection, or trauma?
- Does the patient have any psychiatric disorder?

Age

- At a young age, infectious, inflammatory, epileptic, traumatic, or toxic pathogeneses are more likely
- In elderly, vascular, pharmacological, metabolic, epileptic, medical, or surgical pathogenesis are more likely

Life Habits Age

- Alcohol or drugs (e.g., benzodiazepines) abuses
- Use of toxic substances
- Toxic work environments

Medical History

- Metabolic or general diseases

Table 3.6 Predictive factors of postsurgical delirium

-
- Alcohol abuse
 - Cognitive impairment
 - Severe functional impairment (Karnowsky)
 - Imbalance of presurgical Na, K, glucose
 - Aortic aneurysm surgery
 - Noncardiac thoracic surgery
 - Age >70
-
- Neurological diseases, focal or diffuse, established, or progressive (including dementia)
 - Epilepsy
 - Recent trauma
 - Recent surgery (Table 3.6)
 - Psychiatric illness

Medications History

- Polypharmacy

Neurological Evaluation

Neurological signs that may suggest the diagnosis should be investigated:

- **Neck stiffness** suggests an infectious/inflammatory cerebral disease or subarachnoid hemorrhage
- **Focal Signs** suggest a cerebrovascular disease (e.g., frontal or parietal lesion or expansive pathology or symptomatic epileptic disease)
- **Non-focal motor signs**, such as myoclonus or *flapping tremor*, suggest the diagnosis of metabolic encephalopathies

General Clinical Evaluation

- Temperature: hyperthermia (meningoencephalitis, sepsis)
- General and nutritional conditions, hydration, complexion, hematomas or wounds, metabolic imbalance, CO poisoning, and anemia

- Vegetative signs: intoxications and metabolic imbalance
- Hemodynamic and respiratory parameters: hypertension, hypoxic encephalopathy, hypotension, and shock

Criteria for Identifying the Causes of Delirium

Medication-Induced Delirium

- The assumed drug has effects on the central nervous system.
- Toxic plasma concentration or improvement of clinical picture with dose reduction or drug discontinuation.
- The change in mental status coincides with the time of drug assumption.

Infective Delirium

- There are signs of infection (fever, leukocytosis, elevation of inflammation indexes).
- The change in mental status coincides with the time of infection.

Hydroelectrolytic Imbalance

- There are clinical signs of changes in volemia (history of diarrhea, vomiting, etc.).
- The disorder is confirmed by laboratory findings.

Endocrine Metabolic Disorders (Uremia, Liver Encephalopathy, Hypoglycemia, Hyperthyroidism, and Adrenal Insufficiency)

- The disorder is confirmed by laboratory findings.
- The change in mental state coincides with the time of disorder.

Intracranial Disorders

- Clinical evidence, from medical history and/or physical examination, of an intracranial pathology (ischemic stroke, transient ischemic attack, intracranial hemorrhage, cerebral edema, subdural hematoma, neoplasia/metastasis, meningitis, and non-convulsive epilepsy)

- Objective instrumental evidence confirming the event or, in transient ischemic attack, a history of similar events, or multiple vascular risk factors
- The modification of the mental state coincides with the time of the disorder

Cardiopulmonary Impairment and/or Hypoxia

- Clinical evidence of low cardiac output, pulmonary impairment or cerebral hypoperfusion
- Evidence from blood gas analysis, laboratory tests, ECG/echocardiogram or from radiological cardiopulmonary impairment
- The modification of the mental state coincides with the time of the cardiopulmonary disorder

Alcohol and Withdrawal Syndrome

- Recent consumption of alcohol or sedative-hypnotic drugs or toxic substances, with a history of chronic use
- Evidence of withdrawal crisis
- The delirium occurs in the first week of withdrawal

Preexisting Dementia, Whether or Not Associated with Visual and Auditory Impairment

- The mental state improves with orienting stimuli.
- The mental state worsens with changes in the environment or it occurs mainly at night.

Differential Diagnosis

The following diseases are to be considered in differential diagnosis [3]:

- Acute psychosis.
- Depression
 - 41% of delirium can be misdiagnosed as depression.
- Dementia:
 - Alzheimer's disease.

- ❑ Lewy body disease (not infrequently may manifest characteristic cognitive fluctuations as episodes of delirium without an identifiable medical cause).
- ❑ Vascular dementia.
- Acute cerebrovascular disease with aphasia.
- Other degenerative CNS diseases (e.g., hallucinations during Parkinson's disease).
- Complex partial seizures.

It should always be borne in mind that a confusion state can complicate dementia [32]. From a systematic review of 14 studies, the prevalence of delirium superimposed on dementia ranged from 22% to 89% of elderly patients with dementia. This was associated with an acceleration of cognitive and functional decline, an increase in institutionalization, rehospitalization, and an increase in mortality [33], especially in Lewy's body dementia [34]. In a large, recently published Italian hospital case study, more than 50% of the elderly with delirium had a history of dementia and more than 50% of the elderly with dementia had delirium. The presence of delirium, with or without dementia, but not the presence of dementia without delirium was associated with an increased risk of in-hospital mortality [35].

The conventional and quantitative EEG can allow the early detection of an encephalopathy/encephalitis and allows the differential diagnosis between delirium and senile dementia (Table 3.7) [36].

Table 3.7 Comparative clinical features in differential diagnostics [37]

Clinical features	Delirium	Dementia	Depression	Psychosis
Acute changes in mental state	+	—	—	+
Inattention	+	+	+	+
Impairment of consciousness	+	—	—	—
Disorganized thinking	+	+	—	+
Altered psychomotor activity	+	+	+	+
Chronic duration	+	+	+	+

Diagnostic (Laboratory, Radiology, and Neuropathophysiology) Procedures

Laboratory and Blood Gases

- Change in blood chemistry (metabolic, electrolytic, infectious disorders); hypoxic encephalopathy
- Possible hormone tests (suspicion of endocrinopathy)
- Toxicological, blood and urinary screening

Instrumental Investigations

- Brain CT scan:
 - Focal vascular, inflammatory, traumatic, or expansive lesions (acute or established)
 - Diffuse disease, predisposing to delirium
- Brain MRI scan (for selected or uncertain cases):
 - Similar to CT but more sensitive
- Neuroradiological investigations may detect normal patterns, focal (recent or established), or diffuse lesions, or a combination of focal and diffuse lesions
- EEG:
 - Focal, diffuse, or epileptic changes
- CSF:
 - Suspect of meningitis/encephalitis or SAH

Indications to Urgent CT Scan

Recommended when the clinical evaluation does not reveal a clear extraneurological cause [38], or in any case when one of the following condition is present:

- New-onset focal neurological signs
- History of fall during the previous 2 weeks
- GCS <9 or sudden worsening of consciousness compared to hospital admission
- Oral anticoagulant therapy
- Persistent headache
- Fever without evidence of acute medical conditions, before rachicentesis

EEG Features

In most patients with delirium with an organic cause, EEG will show an alteration of the overall electrical activity organization. This alteration is often closely related to the severity of the encephalopathy and its change over time is useful to monitor the effectiveness of therapies.

The “functional” EEG data acquire particular value if correlated with the anatomopathological neuroimaging data. The EEG in particular allows the identification of:

- Status epilepticus as the basis of the confusion, also providing confirmation of the effectiveness of therapy
- The psychogenic origin of the disorders
- Patterns suggestive of metabolic or toxic encephalopathy
- Patterns suggestive of inflammatory encephalopathy

The authors recommend that the EEG should be obtained as soon as possible.

Pharmacological and Non-pharmacological Treatments

Non-pharmacological Interventions

Even in the case of delirium, **prevention** is the best medicine; evidence suggests that it is easier to prevent than to cure delirium. Prevention consists of early detection and aggressive management of known predisposing and precipitating factors [39].

Protocol of Preventive Interventions [40]

- Cognitive impairment: promote orientation providing appropriate information and with clocks and calendars; provide names and roles of professional figures who assist the patient; encourage visits of family members or friends.
- Visual impairment: ensure the availability of glasses.
- Hearing impairment: if available, allow the use of ear amplifiers, remove any earwax plug.

- Dehydration: early detection of hydroelectrolytic imbalances; encourage oral fluid intake.
- Pain: effectively treat painful symptoms.
- Polypharmacy: eliminate unnecessary drugs and check pharmacological interactions.
- Sphincter function: check for the presence of a bladder globe.
- Immobility: allow early mobilization and, when possible, assisted walking. Avoid restraints.
- Complications of immobilization: early diagnosis of bed-sores, pulmonary embolism, urinary tract, and respiratory infections.
- Sleep fragmentation: limit health activities and noise at night.

Environmental Prevention Measures

The environment must:

- Be calm and quiet, with good, not excessive lighting, that, if possible, may avoid shadows (causing illusions). It should promote the maintenance of day-night rhythm.
- Avoid sensory deprivation but remove sudden and annoying noises.
- Encourage orientation (large watches, clearly legible calendars, colors).
- Have the bed buzzer easily accessible.
- Provide familiar objects (photographs, known objects).
- Avoid the presence of two agitated subjects in the same room.
- Avoid bed transfers and changes as much as possible.
- Have specific paths for patients with *wandering*.

Preventive interventions allow for the decrease of delirium incidence in hospitalized older patients by 40 to 53% and of falls by 62% [41, 42]. According to a 2015 meta-analysis, nonpharmacological preventive interventions decrease delirium incidence by 27% and in-hospital falls by 61%, but do not result in a reduced delirium duration, length of stay, and mortality [43]. This has been confirmed by a Cochrane systematic review in 2016 [44]. In contrast, there are no strong data on the efficacy of delirium **treatment** with nonpharmacological interventions [45].

Pharmacological Interventions

As far as delirium **prevention** is concerned, according to the results of two meta-analyses, there is no convincing evidence of efficacy with regard to the use of antipsychotics [44, 46], which is therefore not recommended also in view of their significant adverse effects. Similar results are reported for patients admitted to intensive care [47]. As far as delirium **treatment** is concerned, pharmacological therapies have side effects. **The drugs should therefore only be used if delirium interferes with the prescribed therapy, or if it jeopardizes the safety and the well-being of patient or caregivers.** Comparisons of use versus non-use of specific drug therapies for delirium are scarce and, in the absence of good randomized controlled trials, current protocols have so far relied predominantly on expert opinion [48–51]. In a 2016 meta-analysis [52] of 15 studies, antipsychotics as a group confirmed a greater efficacy in short-term delirium treatment compared to placebo, with a relatively greater efficacy and better tolerability of second generation antipsychotics (olanzapine, risperidone, and quetiapine) than first generation ones (haloperidol, chlorpromazine). Yet, a more recent Cochrane meta-analysis (2018) concludes that, according to the poor quality data available, antipsychotics do not reduce the severity of delirium, do not resolve symptoms neither they affect mortality [53].

In addition, in a randomized clinical trial on the use of atypical antipsychotic drugs in a palliative care setting, subjects treated with oral risperidone or haloperidol had higher delirium scores and were more likely to require treatment discontinuation in comparison with placebo. Subjects in the placebo/nonpharmacological control group had better overall survival than those in the haloperidol group [54].

A recent meta-analysis, with major limitations, indicates that the use of haloperidol associated with intravenous lorazepam is more effective in hyperactive delirium compared to haloperidol alone, but the conclusions are based on a single numerically limited study of advanced neoplastic patients in palliative care [55].

Overall, the data suggest that antipsychotics do not have a pathogenic effect on the duration or severity of delirium but may eventually be used as symptomatic treatment of agitation, therefore limited to cases of hyperactive delirium. Randomized clinical trials in agitation and dementia suggest an advantage (NNT = 5). Side effects may include extrapyramidal signs, hypotension, sedation, and akathisia. The preliminary evaluation of the ECG QT interval for the risk of cardiac arrhythmias is important. In particular, the QTc parameter must be considered (Table 3.8):

- If more than 440 ms (but less than 500): reduce dosages, discontinue any other medication that prolongs QT, and recheck the ECG after a few hours.
- If the QTc is greater than 500 ms: the risks are higher than the benefits.

Typical Antipsychotics

- *Haloperidol*: the minimum effective dose should be used, for example, 0.5–1.0 mg twice daily per os, reducing the dose further when the delirium improves. The initial dose of 0.5 mg can be administered every 4 h until agitation is controlled.
- *Droperidol* can be administered intravenously due to the faster effect. Warning: sedation, hypotension, less antipsychotic effect than haloperidol.

Atypical Antipsychotics

- *Risperidone*: for patients with side effects or contraindications to haloperidol. Initial dose: 0.5 mg twice daily per os.
- *Olanzapine*: starting dose of 2.5 mg in single administration or twice daily per os.
- *Quetiapine*: 25 mg twice daily per os.

Benzodiazepines

They should be avoided, especially those with long half-life. Their effect is faster than neuroleptics' one, with a shorter peak and a more frequent sedation effect; they can paradoxically worsen delirium. They are the drug of choice for alcohol abstinence syndrome and may be useful in **delirium associated with voluptuary drugs intoxication and myoclonus**:

Table 3.8 Neuroleptic drugs used in delirium [56]

Drug	Dose range	Sedation	EPS	QTc length	Comments
Haloperidol IV/IM/PO/NG	Initial dose: 0.5–1 mg repeatable every 4 h until agitation is controlled Max dose: 20 mg/day (only for psychiatric patients), increases the risk of QTc lengthening and ventricular fibrillation	+	+++	+++	Avoid IM if anticoagulants. PO may have less effect on QTc but more EPS. EV off-label for elongation QTc. Can be given regularly or as needed
Risperidone PO/NG/ODT	Initial dose: 0.25–0.5 mg twice a day (lower doses in elderly or with prolonged QTc) Max dose: 2 mg twice a day	+	++	+	To be considered in hypoactive forms. Less sedative, less likely to cause hypotension (less histaminic activity)
Quetiapine PO/NG	Initial dose: 12.5–50 mg twice a day (lower doses in elderly or with prolonged QTc) Max dose: 200 mg twice a day	++	+	++	To be considered in hyperactive and agitated or mixed forms evening higher doses (PM > AM) can improve sleep
Olanzapine PO/NG/ODT	Initial dose: 2.5–5 mg at bedtime Max dose: 20 mg/day	++	++	++	To be considered in hyperactive forms and in the absence of venous access. Higher metabolic and EPS side effects compared to quetiapine

EPS extrapyramidal symptoms; method of administration, IV intravenous, IM intramuscular, PO oral, NG nasogastric tube, ODT orodispersible tablets

- *Lorazepam* 0.5–1 mg IV or PO ($t_{1/2}$ 15–20 h; 0.5–1 mg per os, possible additional doses every 4 h)
- *Midazolam* 1–2 mg IV repeatable for short-term sedation of hyperactive delirium if the patient is monitored (risk of respiratory depression)

Other Drugs

- *Trazodone* 25–100 mg at bedtime

More specifically with regard to **postoperative delirium**, the Guidelines of the American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults (Table 3.9) are available online at <http://www.geriatricscareonline.org>.

Quality Indicators

- % of patients with documented screening for delirium (at least CAM within 24 h)
- % of patients treated for pain (VAS scale: visuospatial scale with score from 0 = no pain to 10 = maximum pain [58])
- % of patients treated with nonpharmacological measures in the first 24–48 h

Table 3.9 American Geriatrics Society clinical practice guidelines for the prevention and treatment of postoperative delirium

Recommendation	Description
Strong	The advantages clearly outweigh the risks or vice versa
Multicomponent nonpharmacological interventions (for prevention)	Multicomponent nonpharmacological interventions delivered by an interdisciplinary team should be administered to at-risk older adults to prevent delirium Includes mobilization and walking, avoidance of physical restrictions, orientation to the surrounding environment, sleep hygiene, adequate oxygenation, nutrition and fluid repletion, pain management, appropriate medication usage, adequate oxygenation, and prevention of constipation

Continued

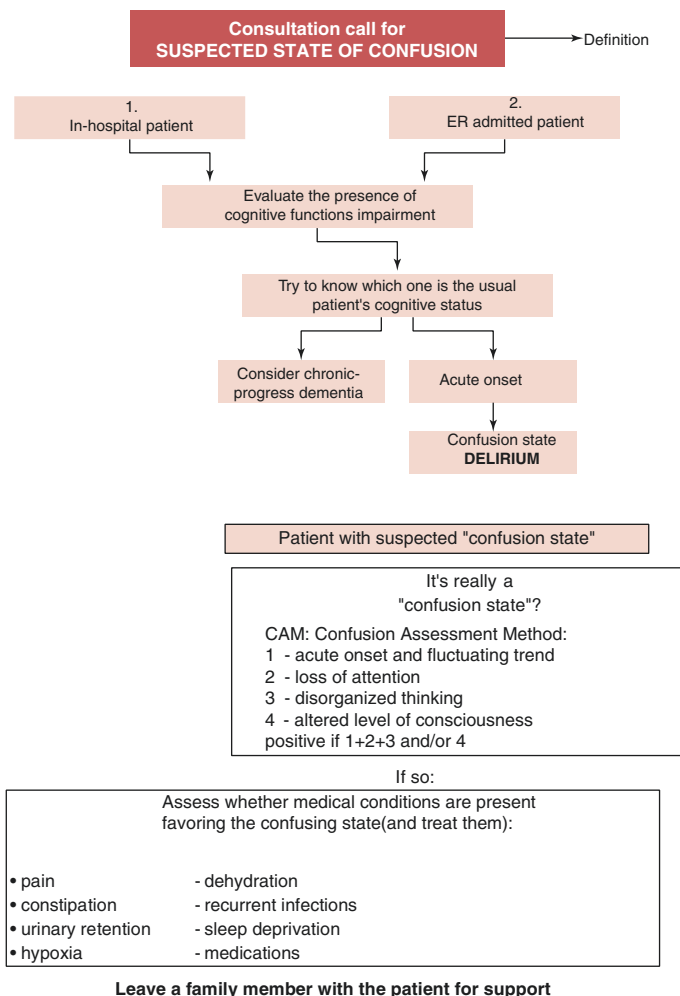
Table 3.9 Continued

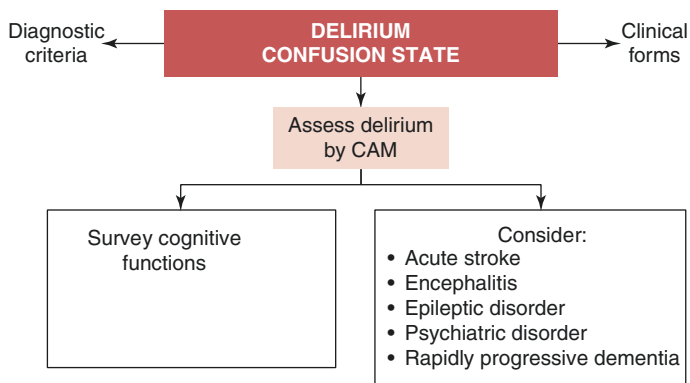
Recommendation	Description
Educational programs	Ongoing, provided for healthcare professionals
Medical evaluation	Identify and manage the organic factors underlying the delirium
Pain management	Should be optimized, preferably with non-opioid drugs
Drugs to avoid	Any drugs associated with the onset of delirium (e.g., high-dose opioids, benzodiazepines, antihistamines, dihydropyridines). Cholinesterase inhibitors should not be prescribed ex novo to prevent or treat postoperative delirium. Benzodiazepines should not be used as a first-line treatment for agitation associated with delirium. Benzodiazepines and antipsychotics should be avoided for the treatment of hypoactive delirium
Weak	There is evidence in favor of such interventions, but the level of evidence or potential risks limit the strength of the recommendation
Multicomponent nonpharmacological interventions	Implemented by an interdisciplinary team when elderly adults are diagnosed with postoperative delirium to improve clinical outcomes
Pain management	Injection of regional anesthetic at the time of surgery and postoperatively to improve pain control, with the aim of preventing delirium
Antipsychotics	The use of antipsychotics (haloperidol, risperidone, olanzapine, quetiapine or ziprasidone) at the lowest effective dose and for the shortest possible duration can be considered to treat delusional patients who are severely agitated, distressed or who threaten substantial harm to themselves, others or both

Translated and adapted by American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults [57]

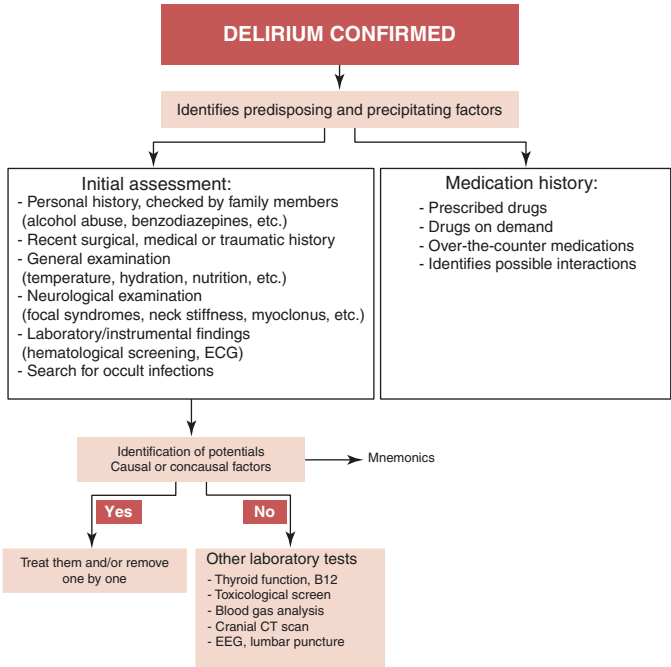
Appendix

Algorithm 3.1 Delirium/Acute Confusion State

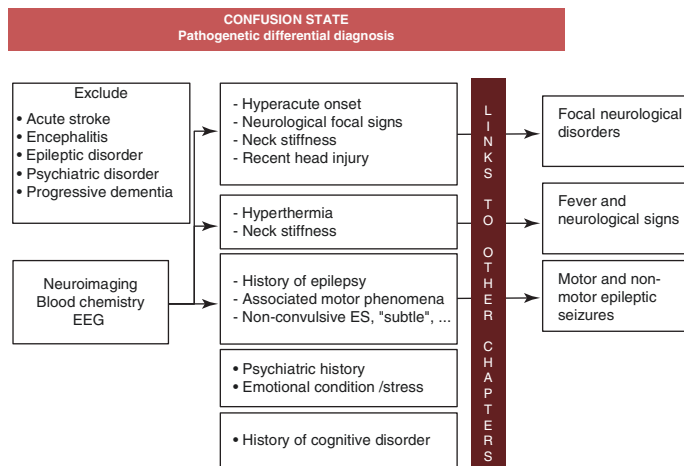


Algorithm 3.2 Delirium/Acute Confusion State

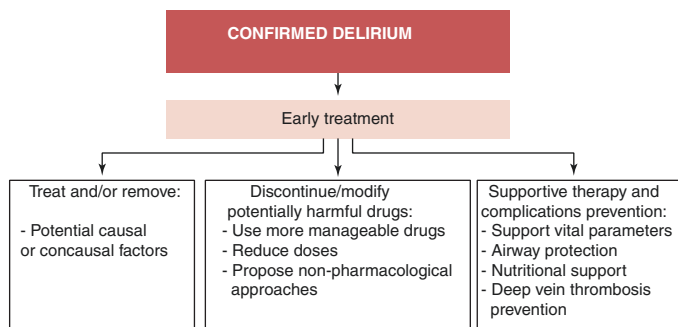
Algorithm 3.3 Delirium/Acute Confusion State



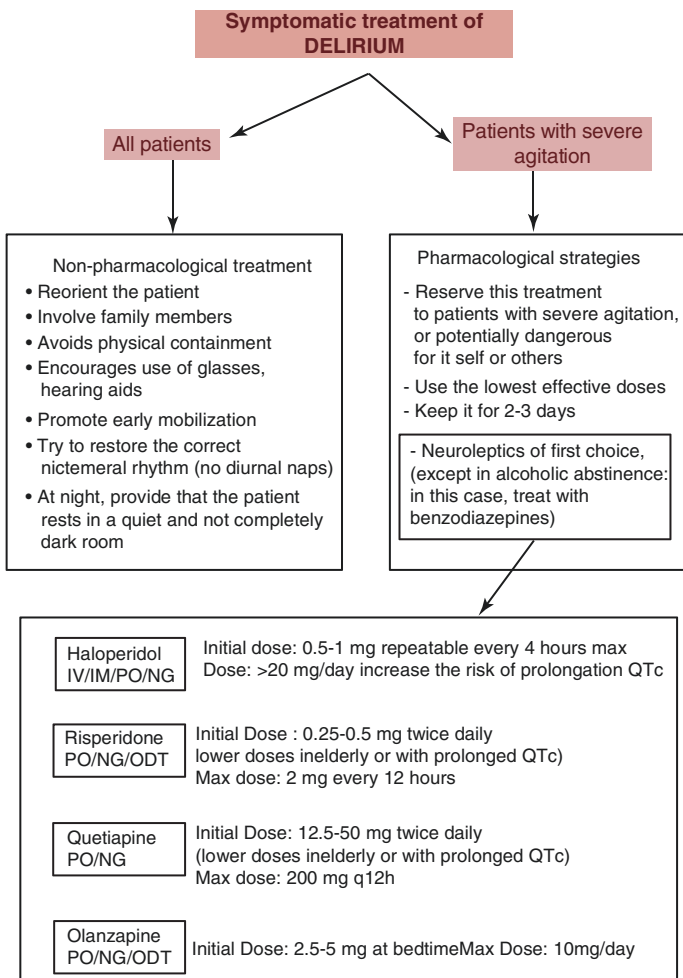
Algorithm 3.4 Delirium/Acute Confusion State



Algorithm 3.5 Delirium/Acute Confusion State



Algorithm 3.6 Delirium/Acute Confusion State



IV: intravenous; IM: intramuscular; PO: oral; NG: nasogastric tube;
ODT: orodispersible tablets

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4.

Motor and Nonmotor Epileptic Seizures

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Introduction

The purpose of the following chapter is to define a diagnostic and therapeutic pathway for epileptic seizures in the setting of emergency care. Therefore, only aspects related to the initial stage of care for patients with probable or suspected recent-onset epileptic seizures will be extensively discussed.

The International League Against Epilepsy (ILAE) recently published (2017) the revised classification of epileptic seizures [1] and epilepsies [2] and, in 2015, the new classification of status epilepticus (SE) [3]. An updated definition of epilepsy has been formulated in 2014 [4], so also this topic will be covered in the following sections.

Definitions

Epileptic seizures are paroxysmal events with sudden onset, caused by abnormal electrical discharges in the brain; they may occur at any age, with tendency to recur, though unpredictably, in most cases. They show a wide range of causes and may represent a sporadic or even isolated clinical manifestation of an underlying disorder; treatment of their etiologies may lead to seizure disappearance.

In many patients, seizures have a chronic course that is independent of the underlying disease and may require long-term treatment, usually with drug therapy. Occasionally, seizures represent a medical emergency, needing urgent care procedures involving multidisciplinary healthcare personnel.

ILAE has defined epileptic seizures as: “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” [5].

Diagnostic approach requires to clearly differentiate between epileptic seizures and epilepsy, and between isolated epileptic seizures and SE.

An **epileptic seizure** should be considered a symptom [6], while **epilepsy** is a condition characterized by recurrence of seizures, a

more or less defined etiology and, in some cases, a predictable long-term prognosis.

It is not possible to formulate absolute semeiological criteria for epileptic seizures [7]. Any neurological sign or symptom can be the manifestation of a seizure. Seizures may comprise symptoms, e.g., of visual or auditory hallucinations, false memories, feelings of fear, etc. [8] Signs and symptoms appearing during a seizure are closely related to its anatomical site of generation. The degree at which the pathological neuronal discharge spreads to other brain regions is usually correlated to the sequential appearance of different manifestations during the same episode.

- *Nonconvulsive seizure*. In rare, but still widely documented cases, it is possible that negative signs or symptoms (aphasia, confusion, etc.) may be the only clinical features observable in a single patient. In particular, these negative symptoms may characterize *nonconvulsive SE*, which must be differentiated from all other delirium-like conditions.
- *Convulsive seizure*. Typically, both seizures and SE present with involuntary motor signs, involving variable body districts, associated to a variable degree of awareness impairment.

In the emergency care setting, the appearance of new symptoms, even if not strictly neurological ones, is considered relevant, when they are contemporary or closely following the seizures (Figs. 4.1 and 4.2).

Figure 4.1 ILAE 2017 classification of epilepsies

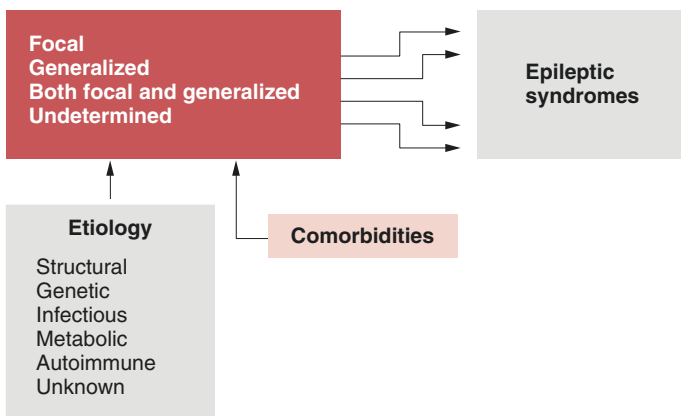
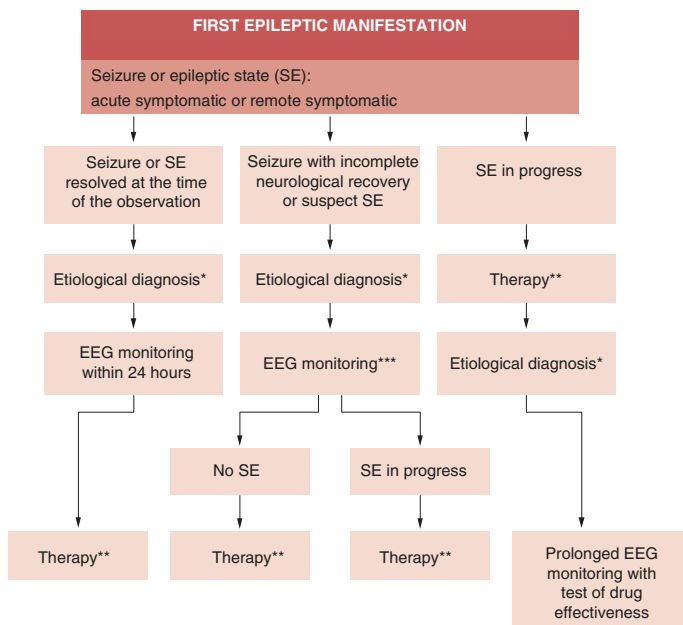


Figure 4.2 Algorithm with time sequence of emergency interventions (first epileptic manifestation)



* See paragraphs *Etiology of epileptic manifestations*,

Triggering factors, Laboratory and instrumental investigations;

** See paragraph *Patient management*;

*** See paragraph *Pharmacological therapy of status epilepticus*

Cardiovascular and respiratory disturbances, as well as symptoms suggesting possible traumatic injuries, should be carefully evaluated, as they are possibly relevant in determining the patient's prognosis.

The new classification of epileptic seizures [1] divides them into focal onset, generalized onset, and unknown onset seizures (Table 4.1). Focal onset seizures may, or may not, be characterized by an impairment of awareness, and may, or may not, evolve to bilateral tonic-clonic seizures. The initial sign or symptom determines the classification of the seizure overall. The appearance, at any time during the episode, of impairment of awareness prompts classification as "seizure with impaired awareness."

Table 4.1 ILAE 2017 seizure classification (reduced version)

Focal onset	Generalized onset	Undefined onset
Motor vs nonmotor onset Conserved vs impaired awareness Evolution from focal to bilateral tonic-clonic	Motor vs nonmotor onset (absences)	Motor vs nonmotor onset
Unclassifiable seizures		

Likewise, epilepsies can be classified as generalized, focal, or with both generalized and focal seizures. In this classification, patients diagnosed with epilepsy are grouped according to the semeiology of seizures and according to the brain regions/networks affected by epileptic discharges.

This classification also entails a further diagnostic level: epileptic syndromes, which are defined by a set of common and homogeneous electro-clinical, prognostic, and sometimes neuroimaging features (Fig. 4.1).

Traditionally, in order to diagnose epilepsy in a patient, it was required to have documented seizure recurrence. In 2014, however, ILAE allowed to formulate the diagnosis in other situations [4]. Therefore, diagnosis of epilepsy (and not of isolated epileptic seizures) has to be considered when:

- At least two unprovoked seizures have occurred with a time interval of more than 24 h between them.
- A single unprovoked seizure has occurred, with a 10-year seizure recurrence risk comparable to the risk observed after two unprovoked seizures (at least 60%).
- The seizure clearly appears to be part of an epileptic syndrome.

It should be noted that two or more epileptic manifestations (isolated seizures or SE) occurring within 24 h should be considered as a single episode.

After a first unprovoked seizure, the risk of recurrence varies between 40% and 52% (32% during the first year and 46% at 5 years) [9]. This risk increases if:

- The seizure is related to a preexisting brain injury.
- EEG shows epileptiform abnormalities.

- There are neuroimaging abnormalities.
- The seizure occurred during sleep.

The distinction between **single seizure** and **SE** is fundamental for the implications on antiepileptic therapy, because an actual indication for emergency treatment is recognized only for the latter [10]. The most recent ILAE classification provides a conceptual definition of SE, which only partially provides operational parameters: “SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point T1). It is a condition, which can have long-term consequences (after time point T2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.” A further clarification of T1 and T2 concepts is reported in the following paragraph on SE therapy.

A diagnosis of SE can be reasonably formulated in the following two situations:

- Continuous epileptic manifestations lasting more than 20–30 min, or two or more seizures within 30 min without complete interictal neurological recovery [11].
- In the case of continuous generalized convulsive manifestations, it is believed that the diagnosis of SE can be made even after 5–10 min, without delaying treatment start [10].

The new classification introduces description of the patient by axes. The correct identification of the fundamental features of SE (semeiology, etiology, EEG features, and patient age) is often only feasible in the acute setting and can provide essential elements for prognosis and therapy. As explained below in the therapy section, this classification helps determine the indications for treatment, according to the type of SE (Table 4.2).

Two further elements are particularly important, in the emergency medical setting, for prognosis and therapy:

- The distinction between **known epileptic condition** and **unknown epileptic condition** [12] (Figs. 4.2 and 4.3), also with regard to SE [13]
- The differentiation between **acute** and **remote symptomatic** seizures

Table 4.2 ILAE 2015 classification of status epilepticus

The SE has to be described on the basis of four axes	
<ul style="list-style-type: none">• Semeiology• Etiology• EEG features• Age	
AXIS 1—Semeiology	
<ul style="list-style-type: none">– With prominent motor symptoms<ul style="list-style-type: none">– Generalized convulsive– Myoclonic– Focal tonic– Hyperkinetic– With prominent motor symptoms<ul style="list-style-type: none">– Nonconvulsive in coma patients– Nonconvulsive without coma	
AXIS 2—Etiology	
(ILAE 2015 Version)	
<ul style="list-style-type: none">– Known etiology<ul style="list-style-type: none">– Remote– Progressive– Within defined epileptic syndromes– Unknown etiology	
(Alternative Version) ^a	
SE in patients with known history of epilepsy:	
<ul style="list-style-type: none">– With triggering factors– As part of specific epileptic syndromes	
SE in patients with or without history of epilepsy:	
<ul style="list-style-type: none">– Acute– Remote– Progressive	
SE with unknown etiology (cryptogenic)	

Continued

Table 4.2 Continued

AXIS 3—EEG Features	
–	Anatomical site of abnormalities
–	Pattern
–	Morphology
–	Temporal trend
–	Response to stimuli
–	Drug-induced changes
AXIS 4—Age	
–	Neonatal (0–30 days)
–	Infant (1 month–2 years)
–	Children (from 2 to 12 years)
–	Adolescents and adults (12 to 60 years)
–	Elderly (>60 years)

^aProposal of the Epilepsy Study Group of the Italian Society of Neurology

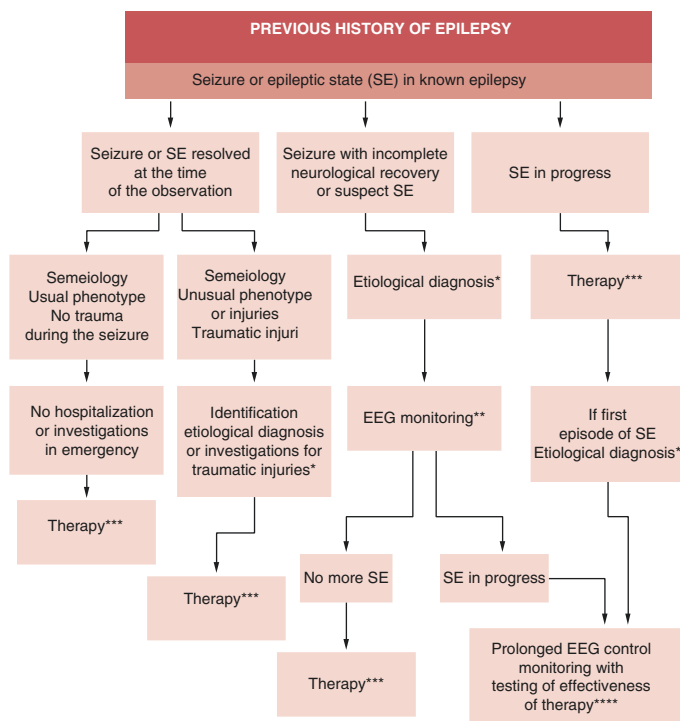
The latter classification is made on the basis of the time interval between the onset of the underlying disease and the appearance of epileptic seizures. This time interval is not equal for all disorders, but an interval of less than 7 days prompts classification of the seizure or the SE as “acute symptomatic.” In the case of “remote symptomatic” seizures, the initial cause (e.g., malignancy, stroke, etc.) may differ from the actual triggering factor (hyperthermia, electrolyte disorder, seizure-facilitating therapies, etc.).

Differential Diagnosis

The differential diagnosis with other causes of paroxysmal neurological events most frequently includes:

- Presyncope (or lipothymia) and syncope (see Chap. 1)
- TIA, drop attacks, transient global amnesia, etc. (see Chap. 10)
- Non-epileptic psychogenic seizures (see Chap. 17)
- Paroxysmal sleep disorders (REM behavior disorders, parasomnias, restless legs syndrome, etc.)
- Movement disorders (dystonia, dyskinesia, etc.) (see Chap. 14)
- Other (migraine, paroxysmal dizziness, etc.) (see Chaps. 5 and 8)

Figure 4.3 Algorithm with time sequence of emergency interventions (patient with known epilepsy)



* See paragraphs *Etiology of epileptic manifestations, Favourable factors, Laboratory and instrumental diagnostics*; ** See paragraph *Patient management*; *** See paragraph *Pharmacological therapy of the epileptic state*; **** See paragraphs *Pharmacological therapy of the epileptic state, Patient management*

Etiology of Epileptic Seizures

In patients with new-onset seizures, etiological diagnosis is essential [14]. Almost every disease featuring focal lesions or widespread involvement of CNS can give rise to isolated or recurrent

epileptic seizures, or to SE. Systemic metabolic imbalances too can present with epileptic seizures. The most common etiologies are:

- Primary CNS disorders (stroke, malignancy, trauma, hypoxia, vascular disorders).
- Metabolic diseases (hypoglycemia/hyperglycemia, hyponatremia/hyponatremia, hypercalcemia, liver encephalopathy).
- Drug intoxication (alcohol withdrawal, cocaine, isoniazid, theophylline, phosphoric esters, etc.) [15].
- Infectious diseases of CNS. Notably, neurocysticercosis and malaria are common causes of seizures in the developing countries; they should be carefully considered in patients with history of recent travel to developing countries or recent immigration.

Triggering Factors

In patients with known history of non-refractory epilepsy, the most common cause of new seizures is the presence of subtherapeutic blood concentration of antiepileptic drugs, that may be related to:

- Patient noncompliance
- Systemic imbalance that may interfere with drug absorption, distribution, and metabolism (e.g., infection)
- Negative pharmacokinetic interactions with other drugs

In addition, multiple factors, including stress, lack of sleep, and caffeine abuse can contribute to triggering seizures in patients with a known history of epilepsy.

Laboratory and Instrumental Investigations

Laboratory Investigations

The clinical picture of single patients should determine the choice of further investigations [16]. Multiple studies have shown a low diagnostic yield for unspecific laboratory tests in the evaluation of a patient with a first seizure. According to literature data, laboratory analyses such as blood count, blood glucose, electrolytes, etc. are abnormal in around 15% of the subjects examined. However, the abnormalities found were mostly incidental or nonsignificant. International guidelines recommend, in the evaluation of adults with first seizure, testing:

- Serum glucose level
- Serum levels of plasma electrolytes (e.g., hyponatremia may be a side effect of some antiepileptic drugs)
- Pregnancy test in women of childbearing age

Other tests may be performed, according to clinical judgment, on the basis of history and symptoms.

- For patients with known epilepsy, who are currently receiving a drug treatment, it is useful to assess blood levels of antiepileptic drugs, although tests are often not available for the most novel drugs in many institutions.
- There is no evidence to suggest that toxicological tests significantly impact on patient outcome. They may be useful for planning further medical and psychiatric care.
- Blood gas test appears to be of clinical utility for patients with generalized convulsive SE, since it may show metabolic acidosis, which is most often spontaneously reversible after the termination of convulsive seizures.

Neuroimaging

Computed Tomography Imaging

For patients with new-onset epileptic seizures and for those presenting with SE, brain computed tomography (CT) scan is the imaging study of first choice in the emergency department, due to its wide availability and its ability to identify underlying disorders, mostly those of surgical interest.

In the light of its easy availability and speed of execution, CT scan is strongly recommended in urgent care setting, in case of first epileptic manifestation.

For patients with known epilepsy, the need for a CT scan should be considered in the presence of any of these conditions:

- New-onset neurological deficits, pointing to a focal or diffuse CNS disorder
- Trauma
- Persistent fever
- Changes in seizure phenotype

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the most accurate diagnostic technique available, due to its high spatial resolution and ability to identify specific features of individual diseases. However, performing a MRI scan in emergency setting may be difficult, due to long time of acquisition and image processing, and for economical or logistical reasons.

Other Tests

Electrocardiogram

Electrocardiogram (ECG) should be considered in many patients; it is often routinely recorded in the emergency department. Especially in the case of loss of consciousness, it is useful for differential diagnosis (syncope associated with rhythm disturbances). Moreover, epileptic seizures can be triggered by a cerebral hypoperfusion resulting from a cardiac disorder. The ECG can easily identify the following situations:

- Prolonged QTc
- Enlargement of the QRS complex
- Prominent R wave in the aVR derivation
- Heart block

Lumbar Puncture

Lumbar puncture should be considered for patients with:

- Compromised immune function
- Persistent fever
- Severe headache
- Persistent alteration of mental state

Electroencephalogram

An emergency electroencephalogram (EEG) should be performed within 1 h from the request (preferably requested by a neurologist) and should ideally be available 24 h a day and 7 days a week, with immediate medical report.

Unfortunately, EEG as described is available only in a few institutions. However, scientific literature considers EEG indispensable for a proper diagnostic and therapeutic strategy in the urgent care for epileptic patients. As mentioned before in the context of the new classification of SE, a thorough description of abnormalities found in EEG is crucial.

Finally, in patients with disorders of consciousness and wakefulness, EEG frequently provides etiological information and is also crucial for differential diagnosis with other disorders presenting with similar clinical pictures.

Status Epilepticus

As shown in the flowchart, EEG is the only instrumental technique allowing to confirm the anamnestic and clinical hypothesis of abnormal electrical discharges, resolved, or still ongoing.

Performing EEG in emergency care is considered fundamental for the diagnosis of convulsive and, especially, nonconvulsive SE, but also to monitor treatment outcome of any SE, if the patient's neurological recovery is not complete. A 30-min recording is sufficient to exclude a diagnosis of nonconvulsive SE. To monitor treatment outcome, execution times cannot be estimated in advance, and if possible it is suggested to perform prolonged EEG monitoring until resolution of the symptoms.

Single Seizures

There is little evidence in the literature that emergency EEG is actually useful in this clinical setting. It is relatively well established that EEG after a single seizure may provide useful information to confirm the diagnosis of epileptic seizure and to identify the type of epilepsy, if performed within 24 h from the seizure (especially in pediatric cases).

Particular attention should be paid to the evaluation of the postictal neurological status, which is not always associated with obvious clinical symptoms. In this case, EEG may detect paucisymptomatic ictal discharges or subclinical epileptiform abnormalities.

Therapy

General Criteria

Mortality is highest in convulsive SE lasting over 60 min. In addition, it is possible that SE may reduce the effectiveness of some drugs over time (in particular benzodiazepines). For these reasons, the treatment of SE is considered a neurological emergency.

The most recent classification of SE [3] has introduced a new concept of fundamental importance in the approach to emergency care. Assuming that not all SE have the same potential to produce a CNS damage, for the first time it has been established that, depending on the clinical features of SE, there are different time-frames for intervention and different levels of care intensity. For the three types of SE shown, Table 4.3 shows the estimated time to treatment start (T1) and the time limit to achieve complete seizure control (T2) in order to prevent damage to CNS.

Medical care should be tailored to each patient presenting with seizures [10]. In the emergency setting, the greatest difficulties are found in the differential diagnosis between epileptic seizures and non-epileptic paroxysmal events. Useful clues for diagnosis include clear evidence of tonic-clonic movements, the presence of postictal confusion, and tongue bite.

It is essential to attempt to obtain a detailed account of the episode from the patient and/or witnesses.

For those presenting with a known history of epilepsy and no ongoing seizures at the time of medical evaluation, only supportive therapy is sufficient.

Table 4.3 Relationship between SE semeiology (type of SE) intervention time (T1) and likely start of damage (T2)

Type of SE	T1	T2
Tonic-clonic SE	5 min	30 min
Focal SE without impairment of consciousness	10 min	>60 min
Absence SE	10–15 min	Not known, perhaps absent risk

In case of single seizure, when inadequate blood levels of antiepileptic drugs are found (if this determination is available), or when there is clear evidence of suboptimal compliance, it is advisable to restart appropriate drug therapy before discharge. This can take place with single-day observation, unless the seizure phenotype is different from the usual for that patient.

Patient Management

Management priorities are defined by ABC emergency criteria, including oxygen delivery and airway assessment, as well as evaluation of body temperature, blood glucose, and measures to prevent secondary brain damage [16].

Intravenous access must be obtained for almost all patients (it may be deferred in subjects with simple febrile convulsions).

If seizures are still ongoing at the time of admission to the emergency department, the ABC sequence will be as follows:

- Airway management:
 - Administration of oxygen
 - For patients with generalized convulsive SE or with cyanosis, endotracheal intubation should be strongly considered:
 - If intubation is warranted, short-term neuromuscular blocking agents should be used for intubation, to ensure that subsequent seizure activity is not masked.
 - Consider EEG monitoring in emergency department if the patient has received neuromuscular blocking agents, since there are no alternative methods to determine if seizure activity is still ongoing.
- Guarantee adequate intravenous access.
- Test blood glucose level and get appropriate correction if needed.
- Consider use of antibiotics, with or without antiviral agents, depending on the clinical situation.
- Treatment goal is to control seizures before neuronal damage occurs (theoretically between 20 min and 1 h).

Antiepileptic Drugs in Emergency Care [17–19]

Currently in Italy only a few drugs are registered with specific indication for SE. Even though the scientific literature strongly supports their use, only lorazepam, diazepam, phenytoin, and phenobarbital are currently registered.

Midazolam in adults is registered in Italy for prolonged seizures in patients already treated in pediatric age with oromucosal midazolam formulations.

Initial SE

Prehospital Management

- *Diazepam* (level A)
 - ☐ Route of administration: rectal
 - ☐ Dosage: 0.2–0.5 mg/kg, max dose 10 mg
- *Midazolam* (level A)
 - ☐ Route of administration: buccal or intranasal [20]
 - ☐ Dosage: 10 mg if body weight >40 kg, 5 mg if weight ≤40 kg in a single dose

Intrahospital Therapy

- *Lorazepam*
 - ☐ Route of administration: i.v.
 - ☐ Dosage: 0.1 mg/kg, max dose 4 mg, repeatable once
- *Diazepam*
 - ☐ Route of administration: i.v.
 - ☐ Dosage: 0.15–0.2 mg/kg, max dose 10 mg, repeatable once
- *Midazolam*
 - ☐ Route of administration: i.v. or i.m. [21]
 - ☐ Dosage: 10 mg if weight >40 kg, 5 mg if weight ≤40 kg, in single dose

Defined SE

When benzodiazepines fail to control seizures, possible choices include:

- **Phenytoin** [22–25]

- It is generally considered the first choice as a second-line therapy in patients with ongoing seizures despite aggressive therapy with benzodiazepines.
- Recommended loading dose is 15–18 mg/kg, which may be increased of further 5 mg/kg if a complete seizure control is not achieved.
- Maximum infusion rate 50 mg/min to reduce the risk of hypotension and cardiac arrhythmias (which has been associated also to the propylene glycol diluting agent).
- If diluted, max concentration 5–10 mg/ml; **never dilute in glucose**.
- Blood level monitoring is particularly useful for this drug considering its nonlinear kinetics.
- Fosphenytoin, a precursor of phenytoin, can be administered also i.m. and is considered safer than phenytoin since it does not contain propylene glycol [25]. It is not currently available in Italy.
- Contraindications: atrioventricular blockade, bradycardia, and severe hypotension.
- Notes:
 - (a) Provide independent venous access on large vessel to reduce the risk of phlebitis.
 - (b) Heart rate and blood pressure should be monitored.
- **Valproic acid** [26]
 - Loading dose: 20–40 mg/kg, maximum dose 3000 mg.
 - Maximum infusion rate: 6 mg/kg/min.
 - Valproic acid has an excellent safety profile.
 - Contraindications: liver dysfunction, mitochondrial diseases, and hepatic porphyria.
 - Notes:
 - (a) Risk of liver and pancreatic toxicity.
 - (b) May cause thrombocytopenia and platelet aggregation dysfunction (caution with intracranial bleeding) [27].
- **Levetiracetam**
 - Loading dose: 40–60 mg/kg, maximum dose 4500 mg.
 - Maximum infusion rate: 500 mg/min.
 - Contraindications: severe renal failure.

- ☐ No cardiocirculatory side effects.
- ☐ Low risk of worsening level of awareness.
- ☐ Notes:
 - (a) In case of renal failure, the dose should be reduced according to the degree of renal function.
 - (b) It is dialyzed: in patients receiving hemodialysis, every 4 h of dialysis administer an additional dose of 250–500 mg.

■ **Phenobarbital**

- ☐ Shows an efficacy similar to lorazepam.
- ☐ Mostly used in Italy for neonatal SE.
- ☐ Recommended loading dose: 10 mg/kg (maximum 20 mg/kg) i.v.
- ☐ Maximum infusion rate: 50 mg/min.
- ☐ Contraindications: porphyria, liver failure, severe heart disease, and severe respiratory depression.
- ☐ Notes:
 - (a) Requires cardiorespiratory monitoring
 - (b) It may provoke hypotension

Other Drugs [28]

■ **Lacosamide**

- ☐ Dose: 200–400 mg in a single dose, maximum dose 600 mg
- ☐ Maximum infusion rate: 50 mg/min
- ☐ Contraindications: Atrioventricular blockade of II-III degree
- ☐ Few reports in literature; actual effectiveness still to be determined
- ☐ Notes:
 - (a) Especially for doses above 400 mg, monitor ECG, in case of simultaneous administration of drugs that lengthen the PR interval
 - (b) It has no significant pharmacokinetic interactions

■ **Topiramate**

- ☐ Dose 300–600 mg/day
- ☐ No parenteral formulation available
- ☐ It has to be administered by nasogastric tube in patients unable to swallow

Nonconvulsive Refractory SE

Nonconvulsive SE is defined by the lack of prominent motor manifestations. Since third-line therapy with anesthetic drugs is associated with important side effects and complications, such an aggressive treatment should be reserved for situations where the physician considers the continuation of the SE a greater risk for the patient than the treatment itself. If it is not the case, a viable option is to use several second-line antiepileptic drugs sequentially.

Recent observational studies have suggested that third-line treatment itself worsens patient outcomes [29, 30]; furthermore, the scientific evidence concerning the timing and extent of neuronal damage secondary to seizures is limited, and mainly concerns convulsive SE [31–33]; therefore, it is believed that the choice of how aggressive the treatment should be has to be individually tailored.

Refractory Convulsive SE

If two or more initial drug therapies fail to control seizures, the next line of treatment includes, in addition to the continuation of second-line drugs, continuous infusion of drugs with proven antiepileptic efficacy but not commonly used in chronic treatment.

These therapies can only be administered with respiratory and cardiovascular assistance and, consequently, are limited to intensive care settings [34]. Clinical and neurophysiological monitoring, however, is in charge of the neurologist assisting the ICU physician in the choice and conduction of treatment [35].

■ Pentobarbital

- ❑ Bolus 1–3 mg/kg (may be repeated) followed by a continuous infusion of 3–5 mg/kg/h
- ❑ Has a powerful antiepileptic action, reduces intracranial pressure, and lowers body temperature
- ❑ Causes severe respiratory and cardiovascular depression, is subject to drug accumulation, and prolongs the recovery time and intubation after weaning
- ❑ Involves risk of paralytic ileum, immunosuppression, lingual edema, and hyponatremia. Induces the CYP P450 system

- ☐ It has faster onset of action compared to phenobarbital, but it is more sedative

■ Midazolam

- ☐ 0.2 mg/kg bolus, at a maximum rate of 4 mg/min (may be repeated), then continuous infusion of 0.05–0.6 mg/kg/h
- ☐ Has rapid action and a good safety profile
- ☐ May be subject to tachyphylaxis, with risk of recurrence of seizures
- ☐ Is the most widely used anesthetic drug, possibly shows lower risk of side effects or toxicity than pentobarbital
- ☐ There is some risk of drug accumulation in obese, elderly, and renal failure patients
- ☐ When EEG monitoring available, consider dose escalation until the seizures disappear. With midazolam monotherapy, it is unlikely that a *burst suppression* EEG trace can be obtained; this result is more easily achieved with association with propofol

■ Propofol

- ☐ Bolus 2–5 mg/kg (may be repeated), then continuous infusion of 2–12 mg/kg/h (caution should be exercised above 5 mg/kg/h)
- ☐ It is a short-acting anesthetic drug and has excellent pharmacokinetics, with rapid action and very short half-life
- ☐ May cause cardiorespiratory depression, involuntary movements and the risk of *Propofol-Infusion-Syndrome* (PRIS), especially if used for prolonged periods (cardiovascular collapse, lactic acidosis, hypertriglyceridemia, and rhabdomyolysis) [36]
- ☐ In case of prolonged infusion (more than 24–48 h) the daily control of pH, CPK and lactates can allow an early diagnosis of PRIS
- ☐ The combination of propofol and midazolam as continuous infusion may reduce the dose needed, thus lowering the risk of side effects with equal effectiveness

In extreme situations, inhalant anesthetics or neurosurgical options may be considered. These topics, however, do not pertain to emergency care.

There is little evidence to guide the choice and mode of use of antiepileptic drugs in acute setting, particularly about how to perform the transition to a chronic drug therapy. It is recommended to adapt the drug therapy to each individual patient, always with the aims of achieving complete control of the SE (not needed for sporadic seizures) and avoiding drug-related toxic effects. Midazolam may be less effective in stopping SE than propofol and pentobarbital, but it carries a lower risk of hypotension.

Setting Up Chronic Drug Therapy

There is no clear evidence about the need of emergency drug therapy in a patient presenting with a single seizure, even with a generalized convulsive one [37].

The FIRST trial concluded that the probability of long-term remission is not affected by the decision of starting treatment after the first seizure. However, this does not exclude the possibility that new seizures may be considered unacceptable; in some clinical situations (e.g., patients with consciousness impairment, or with risk of severe complications in the case of a further generalized convulsive seizure), the recurrence of seizures may complicate or aggravate the clinical picture [38]. The decision of starting or deferring treatment, however, must be taken in agreement with the patient, who has to be informed about the risks. It is useful to restate that increased risk of seizure recurrence is observed when:

- The seizure is related to a preexisting cerebral lesion
- EEG shows epileptiform abnormalities
- There are neuroimaging abnormalities
- The seizure occurred during sleep

The Scottish Intercollegiate Guidelines (SIGN) [39] suggest that it is reasonable to recommend prophylactic antiepileptic drug treatment only if the patient has already had previous seizures.

The MESS study (Medical Research Council Multicentre Study of Early Epilepsy and Single Seizure) [40], which dealt extensively with this aspect of decision-making, recommended in particular that:

- Seizures provoked only by alcohol deprivation, metabolic or pharmacological alterations, or sleep deprivation should not be treated with antiepileptic drugs.
- Patients should not be treated if there is no diagnostic certainty.
- After the first generalized seizure, antiepileptic therapy should be prescribed only when the risk of recurrence is particularly high [41].
- Antiepileptic drugs should not be prescribed straightforwardly in the emergency department, but only after consultation with a neurologist experienced in epilepsy.

Further Patient Care

Continuation of hospitalization. Decisions on the level of therapeutic intensity are based on the clinical severity and on the causes of epileptic seizures.

Most patients with repeated seizures or severe etiology will require close monitoring and intensive treatment of the underlying condition and seizures. Other less serious conditions, but with a high risk of short-term recurrence, require inpatient stay for observation.

Further outpatient treatment. After a first generalized tonic-clonic seizure without complications and with normal emergency workup, the patient may be discharged provided that a short-term follow-up has been arranged with the patient's general practitioner or a neurologist (possibly experienced in epilepsy).

Patients with subtherapeutic levels of epileptic drugs as a probable cause of the recurrence of seizures should receive an adequate correction of the dosing schedule and get a short-term outpatient consultation with their treating neurologist.

Transfer. For patients with diagnostic or therapeutic needs that exceed the possibilities of the treating institution (e.g., no possibility to obtain prolonged EEG monitoring for a patient with refractory SE treated with neuromuscular blocking agents), transfer to another institution with adequate availability should be considered.

Complications. The most common complications include:

- Drug-related side effects
- Tongue bite and traumatic injuries (generally minor) caused by falls during epileptic seizures

The need for airways clearing should be considered. If the patient is hospitalized, adequate precautions must be taken to prevent risk of falls, and subsequent injuries.

Further Issues

Advice to the Patient

If the patient is discharged directly from the emergency department, it is advisable to provide him with some instructions. Consider written instructions, especially for the problem of fitness to drive.

- First of all, the patient must be warned of the possibility of seizure recurrence and of consequent risks, in relation to work activity, motor vehicle driving, etc. In particular, he/she should be reminded that people with diagnosis of epilepsy may be considered fit to drive motor vehicles, according to the Italian law, only after 1 year free from reported seizures. In the case of first provoked seizure (acute symptomatic), no limitations may be placed, while in other cases (non-provoked first seizure), the patient cannot drive motor vehicles for 6 months. These limitations of driving ability are, however, subject to revision at follow-up neurological evaluations.
- Further restrictions of daily activities must be agreed on between the patient and the treating neurologist. Consideration will be taken for different factors, such as seizure and epilepsy type. While this topic does not pertain to emergency setting, it is always useful to suggest patients to carefully evaluate risks related to potential loss of consciousness during daily and working activities.
- In adults, only in certain situations (e.g., repetitive seizure recurrence or SE), it may be advisable to suggest to the patient and family members to keep available a box of rectally administered diazepam (or oral lorazepam or midazolam), in case of short-term recurrence.

- If triggering factors (sleep deprivation, suboptimal compliance to drug therapy, etc.) or clear correlations with stimuli have been identified (e.g., intermittent light stimuli), they should be reported to the patient. Moreover, the patient should be warned, in case of occurrence of minor seizures (e.g., a focal seizure preceding a tonic-clonic generalized one), to obtain shortly an outpatient reevaluation for the appropriate changes to chronic drug therapy.

Medico-legal matters. Doctors caring for patients with seizures should be aware of some medical-legal pitfalls:

- **Nonrecognition of nonconvulsive seizures.** Nonconvulsive SE may be misunderstood or interpreted as a mental disorder or confusional state. EEG is the first-choice diagnostic method to identify this condition.
- **No control of epileptic seizures** reached despite aggressive treatment; it is believed that neurologic dysfunction may arise after 20–30 min of continuous seizure activity, even in the presence of adequate oxygenation and ventilation.
- **Nonrecognition of etiology underlying seizures.** Even if lack of adherence to suggested therapy and subtherapeutical drug levels are among the most common causes of seizures in the emergency setting, screening for eventual infections, or metabolic causes of seizures should be performed when indicated. In patients with adequate drug levels, who are febrile or, e.g., with altered mentation, adequate laboratory, and imaging investigations should be warranted.
- **Sudden unexplained death (SUDEP).** From a legal point of view, it is believed that patients and/or family members should be warned of the increased risk for unexplained sudden death observed in people with epilepsy. Methods of communicating this problem have to be tailored on a case-by-case basis. SUDEP [42] has an incidence ranging from 0.35 per thousand people/year (in patients with new-onset epilepsy and in patients in remission) up to 3–9 per thousand people/year (in patients with chronic refractory epilepsy). Identified risk factors are:
 - The presence of generalized tonic-clonic seizures
 - The onset of epilepsy during childhood
 - A long history of epilepsy
 - Age between 20 and 40 years old

- ❑ Polytherapy with antiepileptic drugs
- ❑ Epilepsy due to possible channelopathy, which may determine both heart disease and epilepsy

Special Situations

Eclampsia (see Chap. 16). Seizures in pregnant women may be a serious complication of untreated preeclampsia [43]. In fact, eclampsia can occur until 4 weeks after birth. Pregnant patients should be treated in the same way as nonpregnant ones, since the risk of seizure-related complications is higher than the risk of antiepileptic drug toxicity. Fortunately, eclamptic seizures are usually of short duration. Magnesium sulfate is the treatment of choice [44].

Trauma. Seizures after traumas can be caused by a number of intracranial injuries and conditions that need to be properly diagnosed [45]. The subsequent risk of developing symptomatic epilepsy is directly related to the severity of the injury, but not significantly affected by early, prophylactic use of antiepileptic drugs [46].

Intracranial hemorrhage. Hemorrhagic stroke carries a higher risk of early seizures compared to brain ischemic lesions. Deep, small intraparenchymal hemorrhages are thought to pose a lower risk, unless they involve temporal regions. Larger hemorrhagic lesions causing mass effect are at higher risk of causing seizures. Still debated in the literature is the indication for prophylactic antiepileptic treatment in these cases.

Alcohol withdrawal seizures. They can occur 6–48 h after cessation of alcohol intake; they are observed with any level of alcohol in the blood. Benzodiazepines are the first-choice therapy; high dosages may be required to control withdrawal symptoms, to prevent or control convulsive seizures [47].

Drug withdrawal seizures. Barbiturate or benzodiazepine withdrawal can cause seizures, also in patients without previous diagnosis of epilepsy. In cases of withdrawal from drugs with long half-life, symptoms may develop days or even weeks after they have been discontinued.

Drug-induced seizures. Overdose of tricyclic antidepressants and isoniazid are two of the most common toxic causes of seizures. The ECG often shows an enlarged QRS and prominent R wave. Treatment of tricyclic overdose requires bicarbonate infusion and supportive therapy. Pyridoxine is the treatment of choice in the case of isoniazid intoxication. Many other drugs (quinolone antibiotics, antipsychotics, amphetamines, etc.) can trigger or precipitate epileptic seizures and should always be considered in the differential diagnosis of first seizure or recent-onset SE.

Traumatic consequences of seizures. Seizures, especially generalized convulsive ones, are often followed by clinical complications, easily missed in the emergency evaluation, with potential medico-legal risks if overlooked.

Around 1–3% of patients admitted to ED for epileptic seizures have bone fractures. Fractures from direct trauma mainly involve the skull, nasal bones, and clavicle; in patients with bone trauma related to the seizure itself, however, the proximal humerus is most commonly affected (dislocations and fractures), together with the vertebrae (up to 3% of generalized seizures in the literature) [48], and acetabular fractures.

A fraction of these traumatic complications may easily go unnoticed and require a high level of suspicion by the physician in charge of the emergency care, especially in the case of elderly patients with possible osteoporosis (sometimes favored itself by antiepileptic drug therapy).

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5. Headache

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Definition

Headache is pain in any region of the head [1]. It is probably the most frequent symptom in medical practice with a lifetime prevalence >90%. It constitutes a common cause of access to emergency department (ED), representing from 1.7% to 4.5% per year of all accesses [2]. Moreover, at the recent ANEU (Italian Association for Emergency Neurology) survey (NEUday 2018), headache was responsible of the 12% of the ED calls covered by neurologists.

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Diagnosis

According to the International Classification of Headache [1], headaches are distinguished in:

- **Primary headaches** (90%), which include migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalalgias, as well as minor forms.
- **Secondary headaches** (10%), which include those attributed to trauma or injury to the head and/or neck, to cranial or cervical vascular disorder, and non-vascular intracranial disorder, those attributed to a substance or its withdrawal, to infections, disorder of homeostasis, attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure and, finally, to psychiatric disorder.

Differential diagnosis of headache is often challenging. Diagnosis of primary headaches is generally clinical (Tables 5.1, 5.2, 5.3 and 5.4). The neurologist is called upon to diagnose the type of headache as accurately and rapidly as possible. Secondary headaches are uncommon, but their recognition is extremely important as timely intervention may be lifesaving. Anamnesis and objective examination are essential. Depending on the clinical suspicion, it may also be necessary to perform neuroimaging [3], in particular **head CT scan (Angio-CT in selected cases)** and/or **lumbar puncture** (LP). LP should be performed preferably using Sprotte needle

Table 5.1 ICHD-3 diagnostic criteria—migraine without aura [1]

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics: <ol style="list-style-type: none"> 1. Unilateral localization 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following: <ol style="list-style-type: none"> 1. Nausea and/or vomiting 2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Table 5.2 ICHD-3 diagnostic criteria—migraine with aura [1]

-
- A. At least two attacks fulfilling criteria B and C
-
- B. One or more of the following fully reversible aura symptoms:
1. Visual
 2. Sensory
 3. Speech and/or language
 4. Motor
 5. Brainstem
 6. Retinal
-
- C. At least three of the following six characteristics:
1. At least one aura symptom spreads gradually over ≥ 5 min
 2. Two or more aura symptoms occur in succession
 3. Each individual aura symptom lasts 5–60 min
 4. At least one aura symptom is unilateral
 5. At least one aura symptom is positive
 6. The aura is accompanied, or followed within 60 min, by headache
-
- D. Not better accounted by another ICHD-3 diagnosis
-

Table 5.3 ICHD-3 diagnostic criteria—hemiplegic migraine [1]

-
- A. Attacks that reflect the criteria for migraine with aura and the underlying criterion B
-
- B. Aura characterized by both of the following symptoms:
1. Fully reversible motor weakness
 2. Fully reversible visual, sensory and/or speech/language symptoms
-

Table 5.4 ICHD-3 diagnostic criteria—cluster headache [1]

-
- A. At least five attacks fulfilling criteria B–D
-
- B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min (when untreated)
-
- C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
 - (a) Conjunctival injection and/or lacrimation
 - (b) Nasal congestion and/or rhinorrhoea
 - (c) Eyelid oedema
 - (d) Facial and frontal sweating
 - (e) Miosis and/or ptosis
 2. A sense of restlessness or agitation
-
- D. Occurring with a frequency between 1 every other day and 8 per day
-
- E. Not better accounted by another ICHD-3 diagnosis
-

Table 5.5 List of the most frequent headache diagnoses in ED

Primary headache
<ul style="list-style-type: none"> • Status Migrainosus • Refractory chronic migraine • Migraine with aura • Cluster headache
Head and/or cervical trauma
<ul style="list-style-type: none"> • Whiplash • Concussion • Epidural/subdural haematoma • Traumatic arterial dissection
Other
<ul style="list-style-type: none"> • Subarachnoid haemorrhage (ESA) • Secondary or idiopathic <i>thunderclap</i> • CSF hypo-/hypertension • Arteritis • Meningitis-encephalitis • Spontaneous arterial dissection • Systemic infections • Hypertensive crisis • Glaucoma • CO poisoning

(atraumatic) to minimize the risk of post LP headache and the possibility of a blood LP due to the procedure. If available, it may be useful to measure CSF opening pressure: values above 250 mm H₂O in supine position may suggest intracranial venous thrombosis or idiopathic intracranial hypertension. In the absence of warfarin, DOAC and/or anti-platelet treatments, a platelet count >40,000 is considered safe to perform a lumbar puncture. For values between 20,000 and 40,000 decide on a case-by-case basis, depending on the risk/benefit. Table 5.5 lists the most frequently encountered headache diagnoses in ED.

In the case of a migraine attack lasting >72 h, the term '**status migrainosus**' is used.

NB. In cases where the migraine aura is associated with motor weakness, an acute ischemic event must be excluded, and in rare cases the diagnosis of hemiplegic migraine is made (see table and Chap. 10).

Signs and Symptoms: Differential Diagnoses

Headache clinical presentation may vary from easily recognizable conditions to others that are vague and misleading, making the diagnosis of malignant headache even more difficult. Symptomatic treatment responsiveness should not be considered diagnostic for a benign headache. However, a potentially life-threatening secondary headache disorder may also be identified based on the patient's description of symptoms and signs. For example, an age over 50 increases the risk of secondary headache fourfold.

Several tools are at the ED physician's disposal to corroborate the headache diagnosis: a careful medical history, a detailed neurological examination and an appropriate diagnostic testing [4, 5].

A few questions are sufficient for a correct anamnestic evaluation:

1. Why did this headache push the patient to ED?
2. Have you presented similar attacks before?
3. When did this type of headache start?
4. How did it start?
5. How long has the headache been at maximum intensity since onset?
6. When did this headache begin?
7. Where is your pain?
8. What kind of pain do you have?
9. What makes it better or worse?
10. What other symptoms are associated with the onset of headache?
11. Are there any other health problems (co-morbidities and/or particular conditions, recent surgical procedures/traumas, treatments, exposure to toxics/drugs/abuse substances)?
12. Do you live in a house with an open heating system (risk of CO poisoning)?

In particular, during the patient's history and evaluation, it is essential to pay attention to symptoms and signs that may be indicative of a secondary headache.

History ‘Red Flags’ suggesting a secondary headache are:

- Sudden onset headache (instantaneously or <5 min suggests scenario type 1 with headache type ‘thunderclap headache’)
- First and worst headache of life, an unusual headache clearly different from those usual in headache patients
- New headache after the age of 50
- Acute headache in conjunction with physical exertion or orgasm
- Acute headache in patients with conditions, co-morbidities and treatments interfering with the haemocoagulative state and/or immune responses (oncohaematological pathology, chronic pathology under immunosuppressive treatment, infectious states, recent infections, recent surgery/trauma, pregnancy and puerperium)
- Recent changes in behaviour and/or performance and/or fluctuations in attention and vigilance
- Neurological symptoms with onset prior to, over or after the painful phase, of a deficient or irritative type (including syncope/convulsive seizures), not compatible with the criteria for migraine aura (see Table 5.2).

‘Red Flags’ on the neurological examination are:

- Altered state of consciousness
- Meningeal signs
- Focal neurological signs
- Fever with or without signs of infection (shaking chills, skin rush)
- Vigilance fluctuations and suggestive behaviour for encephalopathy
- Papilloedema

In particular, attention should be paid to the symptoms and signs of the main non-neurological conditions and conditions that frequently cause secondary headaches: eye diseases, otolaryngologist disease, orthopaedic, internal medicine disease, etc.

In addition, it is important the examination of the vascular system (establish presence and quality of pulses, i.e. carotid artery exam, the temporal wrists, etc.). Painful trigger points in the trigeminal and craniocervical area, the temporomandibular joints and cervical spine (Table 5.6) should be also carefully evaluated.

Table 5.6 Main secondary headaches to be suspected based on warning signs and symptoms [5]

Recommendation	Description
Systemic symptoms including fever	Headache attributed to infection or disorder intracranial non-vascular, carcinoid, pheochromocytoma
History of neoplasm	Brain neoplasm; metastases
Focal and non-focal neurological deficits (including abnormal level of consciousness)	Headaches attributed to intracranial vascular and non-vascular disorders; brain abscess and other infections
Onset of headache is sudden or abrupt	Subarachnoid haemorrhage and other headaches attributed to cervical or cerebral vascular disorders
Age >50 years	Giant cell arteritis and other headaches attributed to cervical or cerebral vascular disorders; neoplasm and other non-vascular intracranial disorders
Pattern change or recent onset of headache	Neoplasm and other intracranial vascular and non-vascular disorders
Papilloedema	Neoplasms and other non-vascular intracranial disorders; intracranial hypertension
Progressive headache with atypical characteristics	Neoplasm and other non-vascular intracranial disorders
Pregnancy or puerperium	Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders (e.g. preeclampsia); cerebral sinus thrombosis; hypothyroidism; anaemia; diabetes
Painful eye with autonomic features	Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome; ophthalmic causes
Post-traumatic headache onset	Acute and chronic post-traumatic headache; subdural haematoma and other headaches attributed to vascular disorder
Immunodeficiency, e.g. HIV	Opportunistic infections
Painkiller overuse or new drug at onset of headache	<i>Medication Overuse Headache</i> ; drug-induced headache

Based on the clinical picture, it is possible to distinguish between patients presenting with ED with headache in four distinct groupings or **clinical scenarios**.

This type of classification allows to set, for each typical situation, the most appropriate diagnostic tests and to stratify the risk (scenarios 1–3 = headache as symptom of life-threatening pathological process vs. scenario 4 = primary headache) [6–9]

Scenarium 1	<p>The patient has a headache that reaches its maximum intensity in less than 1 h with at least one of the following characteristics:</p> <ul style="list-style-type: none"> • Thunderclap headache onset • With neurological signs (focal or non-focal as an altered level of consciousness) • Neck pain or stiffness • With vomiting or syncope at the onset of headache • Headache arising from exertion
Scenarium 2	Severe headache associated with fever and/or neck stiffness
Scenarium 3	<p>No history of headache</p> <p>Recent onset headache</p> <p>Progressively worsening headache</p>
Scenarium 4	<p>History of headache</p> <p>Headache very similar to previous attacks in term of intensity, duration and associated symptoms</p>

The management of the non-traumatic headache ED patient is therefore defined by an algorithm structured on groups of key signs and symptoms, necessary and sufficient to define each of the four **clinical scenarios** that are described in detail below.

Scenario 1: ‘A Sudden Headache’

All adult subjects who go on ED with severe headache (maximum intensity within 1 h of onset):

- With acute onset (thunderclap headache)
- Accompanied by neurological signs (focal or non-focal as altered level of consciousness)
- Neck pain or stiffness
- With vomiting or syncope at the onset of the headache
- Onset with effort
 - They must undergo head CT scan and neurological specialist examination
 - If the head CT scan is normal, or doubtful, or technically inadequate, lumbar puncture must be performed

Table 5.7 ESA locations and causes of bleeding

Traumatic SAH
Temporal and frontal regions
Non-traumatic SAH
Basal cisterns (aneurysm rupture)
Convexity: <ul style="list-style-type: none">• Venous thrombosis (cortical)• PRES/RCVS• Coagulopathies• Cocaine• Lupus vasculitis• Cavernoma• Brain abscess• Amyloid angiopathy/superficial CNS siderosis

The most frightening cause of ‘sudden headache’ to exclude is **sub-arachnoid haemorrhage (SAH)**. **SAH** represents 1–3% of patients with non-traumatic ED headache and is a heterogeneous condition by clinic features, site, and causative factors (Table 5.7).

Only 35–40% of **SAHs** presented with a thunderclap headache. Headache in SAH is not necessarily as ‘the first and worst headache of my life’, but presentation can also be a headache of

non-maximum and hyperacute intensity. The symptoms and signs associated with SAH are headache (74%), nausea or vomiting (77%), syncope (53%) and neurological signs (focal or non-focal, including altered consciousness) (64%). It is associated with neck stiffness only in 35% of cases. [10].

According to **Ottawa Rules** for the identification of SAH (sensitivity 100%; specificity 15.3%) [8, 9], investigate for SAH all patients with ≥ 1 of the following variables:

- Age ≥ 40 years
- Neck pain or stiffness
- Witnessed loss of consciousness
- Onset during exertion
- *Thunderclap headache* (headache that reaches its peak instantly (within 1 s))
- Limitation of neck flexion on examination

Head CT scan is the first-choice test for suspected SAH and should be performed in time for the onset of symptoms. The sensitivity of CT for SAH depends on the machine used, the time elapsed since the onset of symptoms and the experience of the neuroradiologist (Table 5.8) [11, 12].

There is currently insufficient evidence to propose **CT angiography** as the first-choice test for the diagnosis of SAH. CT angiography should be considered in a selected group of patients to exclude

Table 5.8 CT sensitivity for SAH

Sensitivity to documenting an SAH with first generation CT [11]:

- First 24 h: 95%
- Day 3: 74%
- 1 week: 50%
- 2 weeks: 30%
- 3 weeks: almost 0%

Sensitivity in documenting an SAH with a third generation CT [12]:

- Within 6 h: almost 100%
- >6 h: 95%
- 24–48 h: 90%

aneurysmatic SAH or as an alternative to LP when it cannot be performed or can be misinterpreted [13]. Three to four days after bleeding, MRI (T2 FLAIR) is more sensitive than CT in identifying and delineating SAH. It also makes it possible to exclude other secondary causes of headache. However, in an emergency, the use of MRI is limited in small towns and by the time of acquisition [14].

In case of a **positive CT scan** for SAH or other brain injury, it is necessary to seek neurosurgical counselling and to arrange hospitalization according to the diagnosis.

If the **CT scan is negative**, the **LP is** performed at least 6 h after the headache starts [13]. After 12 h it has a sensitivity in detecting SAH of 100% (12 h is the time necessary for erythrocytes to release haemoglobin, and this is transformed into bilirubin) and xanthochromia is detectable up to 2 weeks after the event. The presence of xanthochromia can be assessed by visual inspection. CSF analysis with a spectrophotometric technique can be useful to detect xanthochromia and distinguish the presence of oxyhaemoglobin (released by erythrocytes in the case of traumatic LP contaminated by blood) from bilirubin, which is suggestive of SAH because it is synthesized only in vivo. If a CSF xanthochromia is detected, neurosurgical counselling or hospitalization according to diagnosis must be sought. If the **LP is normal**, the fearsome SAH can be excluded, and other possible causes of *thunderclap headache* [15, 16] should be considered (Table 5.9).

In relation to the many conditions and pathologies recognizable as possible causes of *thunderclap headache*, it will be essential to perform appropriate diagnostic tests and from time to time with respect to the clinical question (or questions) that the neurologist specialist must explain in the request for individual examinations.

For a general address, Table 5.10 shows the main conditions related to secondary *thunderclap headache* grouped in relation to the imaging technique that make it useful to diagnose it.

Idiopathic thunderclap headache is always a **diagnosis based on the exclusion of** all possible causes of secondary *thunderclap headache*.

Table 5.9 Differential diagnosis of the *thunderclap headache* [16]**Most common causes**

- Reversible cerebral vasoconstriction syndrome (RCVS)
- Subarachnoid haemorrhage (SAH)

Less common causes

- Brain infections
- Cerebral sinus venous thrombosis
- Cervical artery dissection
- Complicated sinusitis
- Hypertensive crisis
- Intracerebral haemorrhage
- Ischemic stroke
- Idiopathic intracranial hypotension/hypertension
- Subdural haematoma

Possible causes

- *Thunderclap* idiopathic or primary headache
- Unruptured intracranial aneurysm

Table 5.10 Causes of *thunderclap headache* vs. diagnostic tool**Identifiable with head CT scan**

SAH (CT without contrast within 24 h)

Intraparenchymal haematoma

Intraventricular haemorrhage

Acute subdural haematoma

Cerebral infarction (after 6–12 h)

Tumours (colloid cyst III ventricle)

Acute sinusitis

Identifiable with LP after head CT scan negative

SAH

Meningitis

CT scan and CSF examinations often normal

Intracranial venous thrombosis

Intra-/extracranial spontaneous arterial dissection

Pituitary apoplexy

RCVS with or without PRES

Symptomatic aneurysm without evidence of SAH

Intracranial hypotension

In the presence of conditions that refer to a type 1 scenario, it is essential to proceed along the diagnostic path considering the key elements that point to specific options, checks and procedures, as follows (**see Algorithms-Path Scenario 1**, page 141).

Scenario 2: 'Headache with Fever or Neck Stiffness'

All adult subjects presenting ED with severe headache:

- Associated with fever and/or neck stiffness
- Should be tested with head **CT scan** and **lumbar puncture**

An acute headache, if accompanied by general discomfort, fever and/or neck stiffness, requires a **differential diagnosis** between meningitis, encephalitis, systemic and connective infections. A new headache of any kind in an **immunocompromised patient** requires starting a differential diagnosis pathway between meningitis (chronic, carcinomatous), cerebral abscess, metastasis, toxoplasmosis or other opportunistic infections [17–20].

Therefore, the physician must request head CT scan and/or perform lumbar puncture (LP).

The execution of the LP allows to exclude the SAH by assessing the presence of xanthochromia in the CSF and to identify a brain infection. It is recommended to perform LP in supine position as soon as possible, because the prognosis of bacterial meningitis depends on the timeliness of starting broad-spectrum antibiotic treatment (e.g. ceftriaxone iv 2–4 g/daily), and there are no reliable clinical indicators to distinguish it from benign prognosis viral meningitis. **Head CT scan should be performed prior to LP** if the patient has the following conditions:

- HIV infection or receiving immunosuppressive treatment, or with active chronic inflammatory and/or neoplastic disease
- New onset epileptic seizures
- Focal neurological deficits
- Abnormal level of consciousness

- GCS <12
- Floating state of consciousness with changes in GCS >2
- Papilloedema

An **increase in the amount of cells in the CSF** can be due to numerous conditions:

- 10–200 cells/ μ l (lymphocytes) are suggestive of viral meningitis, neurosyphilis, multiple sclerosis, tumours, cerebral thrombosis
- 200–500/ μ l (mixed cellularity: lymphocytes, neutrophils and monocytes) of tuberculous meningitis, fungal infection, herpesvirus infections of the CNS, toxoplasmosis and brucellosis
- >500/ μ l (mainly granulocytes) of acute bacterial meningitis
- The presence of immature cells on cytological examination is observed in the meningeal localizations of leukaemia or tumours

The **CSF glucose or glycorrhachia** (reference values: 45–80 mg/dl) has about 50–80% (60% on average) of the blood sugar value. A decrease in glycorrhachia is observed in purulent meningitis, because bacteria and leukocytes consume glucose for their metabolic activities as well as fungi and protozoa but may be reduced even in the presence of leptomeningeal carcinomatosis and other non-infectious diseases.

In addition, a high albumin index (normal value <7.5) is observed in inflammatory processes (purulent and tuberculous meningitis), spinal cord tumours (subarachnoid block); a slightly increased value in viral meningitis, encephalitis and diabetic neuropathy [17, 18].

In the case of SAH or CSF positive for CNS infection, neurosurgical or infectious disease consultation is provided. Admission is provided according to the diagnosis. On the contrary, if CT scan and LP are not diagnostic, the neurologist will assess whether hospitalization is necessary or if possible discharge with follow-up at a Headache Centre or other neurology outpatient clinics.

In the presence of conditions that refer to a type 2 scenario, it is essential to proceed along the diagnostic path considering the key elements that point to specific options, checks and procedures, as follows (**see Algorithms-Path Scenario 2**, page 142). **See also Chap. 6.**

Scenario 3: 'New Onset Headache in Non-headache Adults'

All adult subjects:

- With recently onset headache (days or weeks)
- Progressively worsening or persistent (weeks, months)
- Should be subjected to **head CT scan**, an **evaluation of inflammatory index tests**, in addition to routine haematochemical tests

Attention should be paid to a differential diagnosis that takes into account temporal arteritis and an expansive lesion, including the ventricle III colloid cyst which, although rare, is the most common cause of sudden death [21, 22].

Temporal arteritis mainly affects people aged >50 years, among whom it has a very high prevalence [21]. In a patient with recently onset headache, clinical signs suggestive of temporal arteritis are jaw claudication (strongly related to positive biopsy) and abnormal pulse or tenderness of temporal arteries. These signs—in combination—have a sensitivity of 34%, a specificity >99%, and a positive likelihood ratio of 47%. A high ESR value (>30) is very sensitive (99%) but not very specific (50–70%) [23–25]. The C-reactive protein (PCR) is very high. In these cases, the differential diagnosis of possible connectivopathy is needed. However, this clinical scenario deserves urgent brain CT and haematology tests with PCR.

One of the causes of subacute onset headache is **CO intoxication**.

If the CT shows an expansive brain lesion, such as a **ventricle III colloid cyst**, seek neurosurgical consultation or hospitalization based on diagnosis.

When **both CT scan and haematochemical tests are not diagnostic**, the neurologist's task will be to indicate whether hospitalization is necessary or possible discharge with scheduled follow-up at Headache Centre or other territorial specialist.

If conditions refer to a type 3 scenario, it is essential to proceed along the diagnostic path, considering the key elements that point to specific options, checks and procedures, as follows (see **Scenario 3 Algorithm-Path**, p. 143).

Scenario 4: 'The Headache Attack in Known Headache Patient'

All adult subjects with a **history of previous headache**: Who state that the attack is similar to the previous ones in terms of intensity, duration and associated symptoms must underwent:

- Evaluation of vital parameters, neurological examination and haematochemical tests
- If the findings are negative, symptomatic treatment, discharge from ED with indications to general practitioner in the short term and with possible reservation for neurological outpatient or Headache Centre, for long-term follow-up

Patients with recurrent attacks of a **primary headache** come to ED mostly because of the loss of efficacy of the usual symptomatic drugs used.

In adult patients with recurrent headache, already defined as migraine (including the type 'with aura'), without recent substantial changes, without history of seizures, and without new focal signs or symptoms, **neuroimaging is not necessary** [26]. The ED physician requires blood tests based on clinical context and administered symptomatic treatment (see section '**Treatment**' and algorithm).

Apart from the secondary causes of the current headache, it is possible to consider it an idiopathic headache which, as such, has a high probability of recurrence. For this reason, the patient needs a **follow-up reference** to avoid repeated access to the ED. The patient should be followed in a suitable specialist environment

considering that the diagnostic tests available at ED may not be sufficient to exclude other causes of secondary headache, other than life-threatening ones, and it may not be possible in ED to diagnose the type of crisis according to IHS criteria, a prerequisite for treatment according to the guidelines for migraine and other primary headaches.

*See also paragraph Treatment, p. 138 and paragraph **Algorithms: Scenario Route 4 and Therapeutic Algorithm for Acute Migraine Attack**, p. 144 and 145.*

Rating Scales

In the urgency setting, the assessment of headache intensity must be rapid. The most commonly used scale is the numerical rating scale (NRS). It has the advantage of not requiring, for its use, any paper support and assesses the intensity of pain from 0 (no pain) to 10 (the most terrible pain imaginable). By convention, NRS with score 1–3 indicate a mild pain, NRS = 4–7 a medium pain and NRS >8 a severe pain.

Treatment

In **episodic migraine of mild/moderate intensity** the first-choice therapy is acetylsalicylic acid or acetaminophen 1000 mg or NSAIDs (e.g. ibuprofen 600 mg, naproxen 550 mg, diclofenac 50–100 mg), possibly in combination with antiemetic. If necessary, administer additional oral triptan therapy. In case of triptan failure, add injecting NSAIDs possibly in association with antiemetic or steroids iv.

In **moderate/severe migraine** attack, the first-choice drug is the oral triptan. If the triptan fails, add injecting NSAIDs (e.g. ketorolac 30 mg im), possibly in association with antiemetics (e.g. metoclopramide iv) or steroids iv [2, 27–29]. If the analgesic and/or antiemetic therapy is effective, the patient can be discharged with reliance on a local neurologist or the Headache Centre for differential diagnosis and treatment of primary headaches.

If analgesic and/or antiemetic therapy is ineffective, neurological counselling should be sought for differential diagnosis and treatment of primary headaches.

In the case of a **pregnant migraine** woman, acetaminophen 1000 mg is the drug of choice in the management of acute attack. It is considered a safe medication in all quarters of pregnancy, as no damage to the foetus or major or minor abnormalities have been reported. Less safe is the use of NSAIDs, which is contraindicated after the 30th week, because they can cause premature ductal closure with potential pulmonary hypertension, or cause necrotizing enterocolitis, intracranial haemorrhage or inhibit labour in childbirth. Before the 30th week, ibuprofen should be preferred among NSAIDs at doses not exceeding 600 mg/day, because there are studies that support its safety. An acceptable risk is also posed by naproxen and diclofenac. Among the antiemetics, metoclopramide does not produce teratogenic effects and can be used.

There is currently insufficient evidence to define the safety of pregnant triptans. In particularly intense attacks, steroid therapy with magnesium sulphate can be considered.

During **breastfeeding**, the use of acetaminophen 1000 mg should be preferred in the management of acute migraine attacks. NSAIDs, in particular ibuprofen, are also safe. Among triptans, preference should be given to sumatriptan, which has been well studied in breastfeeding, while there is currently insufficient evidence to define the safety of other triptans [30].

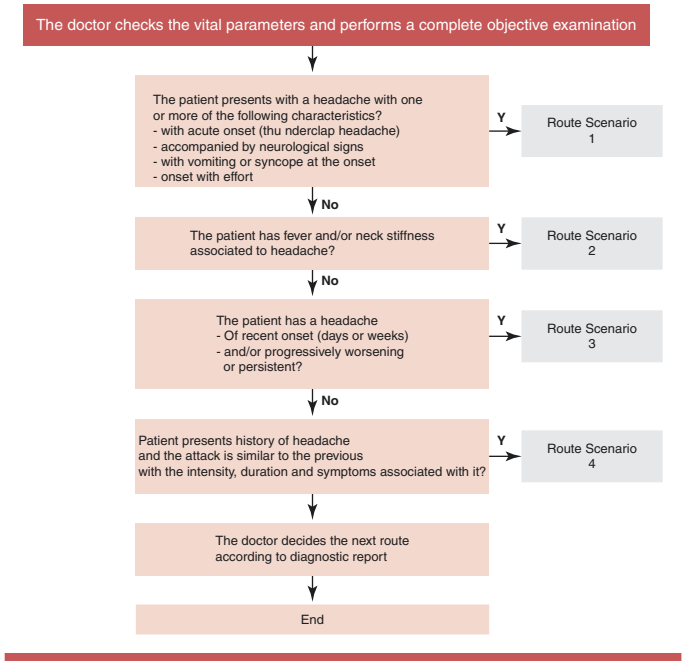
■ For a more extensive treatment of the headache problem in pregnancy and puerperium, please refer to the **Chap. 16**.

For the management of the **acute attack of cluster headache** in ED, oxygen therapy is indicated in adequate quantities (flow rate at 12–15 l/min for 10–15 min) with a mask without a breathing apparatus. It is an effective treatment, fast acting and without side effects. When discharged, recommend the effective and safe sumatriptan 6 mg sc in addition to oxygen as a therapy for the attack [31].

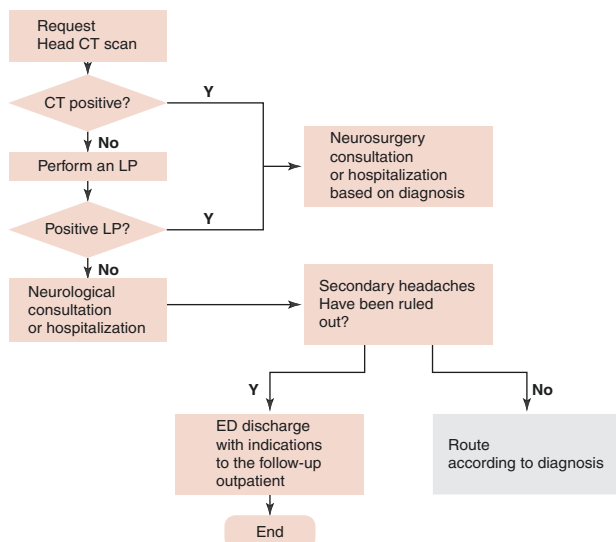
■ See also **Algorithm: Therapeutic Algorithm for Acute Migraine Attack**, p. 145.

Decision Algorithms

Care pathway of adult person who goes in ED for non-traumatic headache



Route Scenario 1



Examinations needed: routine haematochemical tests, coagulation study and head CT scan (this clinical picture always requires an urgent CT, as there are no reliable clinical features to state that an acute onset headache is primary or secondary).

- If **head CT is negative**, perform LPs in the manner provided by the clinic. If the **LP is also negative**, a neurological check is carried out, according to the procedures in use for urgent consultations, to be carried out within 24/48 h, pending which the patient, in relation to the clinical picture, should be kept under **observation**.

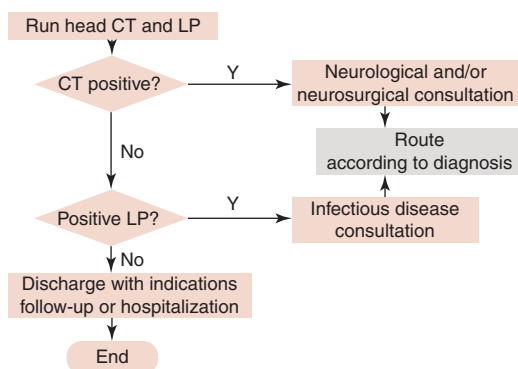
The neurologist will decide whether MRI and/or angio-CT investigations are necessary based on suspected diagnostics (see Table 5.9).

- If **head CT or LP are positive**, request a neurosurgical consultation the patient will continue the therapeutic diagnostic procedure of the secondary headache identified according to the practice in use.

- **If head CT, LP and neurological examination exclude** secondary causes of headache, the patient is referred back to the general practitioner (GP) with the documentation of the investigations performed.

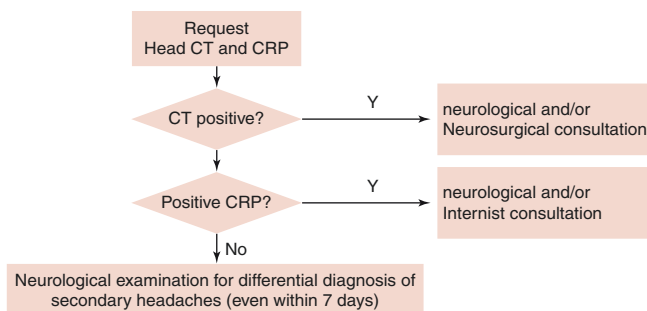
In the absence of specific indications, the choice to perform a CT angiography after negative CT as an alternative to LP is not considered appropriate and should therefore not be recommended.

Route Scenario 2



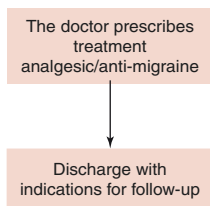
- Urgent request for routine haematochemical tests and coagulation study.
- The doctor requests a head CT scan and performs LP. If brain CT and LP are negative, the patient is discharged and referred to the GP, or hospitalized according to practice.
- If the head CT is positive (for neurosurgical problems), a neurosurgical consultation will be required, and the patient will continue the therapeutic diagnostic procedure of the secondary headache identified according to the practice in use.
- If LP is positive for meningitis, an infectious disease consultation will be required to set up the appropriate therapy and decide the most appropriate ward for hospitalization based on the intensity of care required for the individual case.

Route Scenario 3



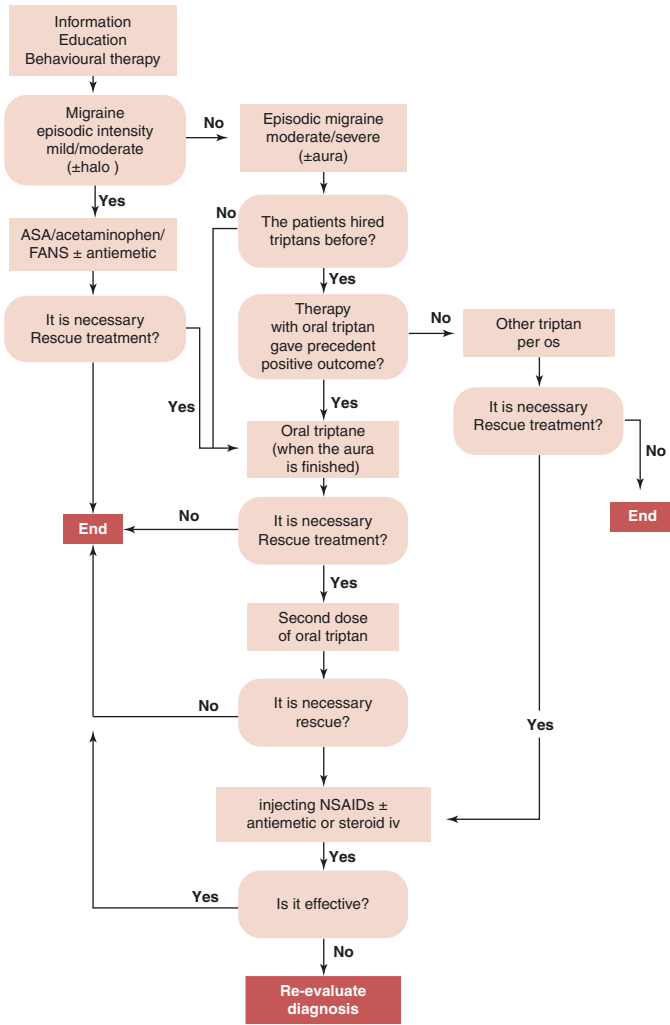
- Request head CT, routine haematochemical tests and PCR assay.
- If head CT is positive (for neurosurgical problems), it requires neurological and/or neurosurgical consultation and the patient will continue the therapeutic diagnostic procedure of the secondary headache identified according to the practice in use.
- If head CT and PCR are negative, or in case of head CT negative and PCR positive, neurological evaluation should exclude secondary pathologies.
- If head CT, PCR and neurological examination exclude secondary causes of headache, the neurologist specialist delivers the report to the patient for submission to the GP.

Route Scenario 4



- Check vital parameters and prescribe analgesic/anti-membrane therapy according to shared protocols in use (Therapeutic Algorithm of Acute Migraine Attack is attached).
- The patient is discharged with a report and entrusted to the GP for subsequent follow-up (according to the Headache Management in General Medicine process).

Therapeutic Algorithm for Acute Migraine Attack



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6. Fever and Neurological Signs

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Submission Methods

- Fever and headache
- Fever and delirium

Fever and Headache

In a recent study, aimed at defining the predictive value of ‘clusters’ of clinical and biological variables depending on the aetiological diagnosis of encephalitis, it was shown that about 90% of

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enrolled patients present at the onset of the disease the syndromic duo **fever + brain** and that more than 65% have an **encephalopathy** variously associated with delirium, seizures and lethargy [1].

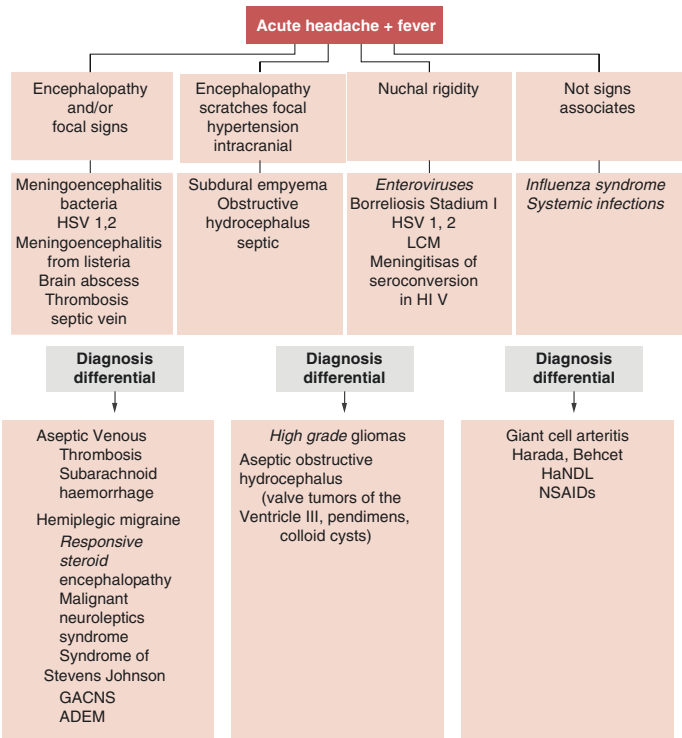
Headache is a very frequent symptom of infection that may be directly related to fever or other factors intrinsic to CNS involvement (stimulation of intracranial allogenic endings through mechanical or chemical actions). Both mechanisms can coexist in the same patient under different septic conditions: brain abscesses, meningoencephalitis and septic obstructive hydrocephalus. The early recognition of this combination of symptoms, although not having a particular etiological specificity, is certainly a sensitive tool for the diagnosis of inflammatory/infectious disease of the central nervous system (CNS) [2, 3].

Figure 6.1 shall be interpreted as a useful tool in terms of urgency and emergency. In the first line of each group are reported the CNS infections that are most frequently observed in our geographical area, in the last line the conditions that may share one or more essential aspects of the clinical picture and that belong to various categories (inflammatory, neoplastic, vascular). As previously pointed out, in case of non-immunocompetence, some infections should be considered, such as encephalitis from HHV6, CMV, toxoplasma, *Cryptococcus*, which have not been reported here and which are not normally present in the immunocompetent patient. Furthermore, chronic infections such as TB and fungal meningoses are not included in the diagram.

Fever, Delirium and Agitation

The literature does not provide systematic studies on the main metabolic/carencial encephalopathies, and in particular on those caused by drug or alcohol abuse/abstinence, which are often accompanied by **fever of varying magnitude and severe systemic and neurological impairment**. The typical paradigm is represented by the drug stimulation/inhibition syndromes of dopaminergic receptors in which hyperthermia is a constant correlate and, generally, dominates the clinical picture (malignant hyperthermia from neuroleptics, acute deprivation syndrome of L-dopa) [6]. In

Figure 6.1 The main syndromic groups: fever and headache



Modified from Marchioni and Minoli [4]
GACNS *granulomatous angitis of the central nervous system*
ADEM *acute disseminated encephalomyelitis*
LCMV *lymphocitic choriomeningitis virus*
HaNDL *syndrome of transient headache and neurologic deficit with Cerebrospinal fluid lymphocytosis. This is a variant of migraine, included in the international classification of headaches (headache attributed to non-vascular intracranial disorder, cod. 7.8), which occurs with mild meningeal signs, lymphomonocytoid pleiocytosis (pleocytosis) and haematoencephalic barrier damage. The recurrence is sporadic, sometimes monophase (monophasic), the cause is unknown. There are no instrumental or (biological) markers or pathognomonic biohumorals. Obviously it represents a diagnosis of exclusion once the absence of viral replication has been demonstrated in the CSF [5]*

these encephalopathies, headache is not a common symptom accompanying fever, but there are other clinical elements or medical history that helps the neurologist to clarify the pathogenetic mechanism. In general, these conditions are characterised by generalised tremors and variable disturbances of the Wakefulness status, which can lead to coma. Particularly in neuroleptic malignant syndrome, hyperthermia is very severe, associated with widespread rigidity and a significant increase in CPKemia. Alcoholic and barbiturate withdrawal syndromes, on the other hand, are dominated by psychic production manifestations with severe hallucinatory syndromes associated with marked agitation and profuse sweating. In all cases the picture can be complicated by generalised tonic-clonic seizures up to the status epilepticus (Figs. 6.2 and 6.3). See also Chap. 3.

Figure 6.2 Main syndromic groups: fever, delirium and anxiety. In group 1a, hyperthermia represents the principal sign of the clinical picture; in the group 1b, fever is frequently present, in particular at the symptoms onset; in the group 1c, it could be present but should be considered an aspecific and ancillary part of the clinical spectrum

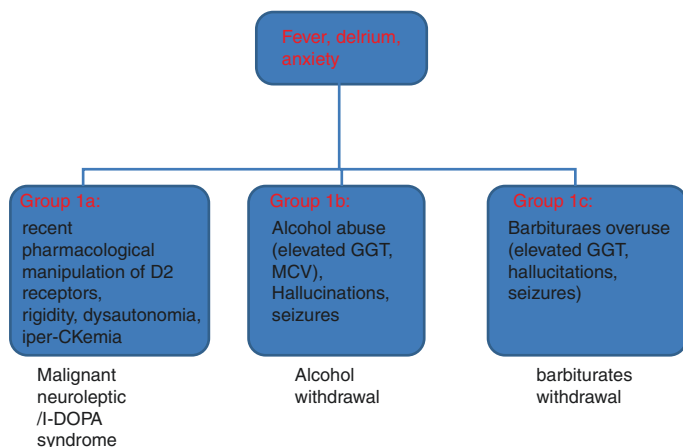
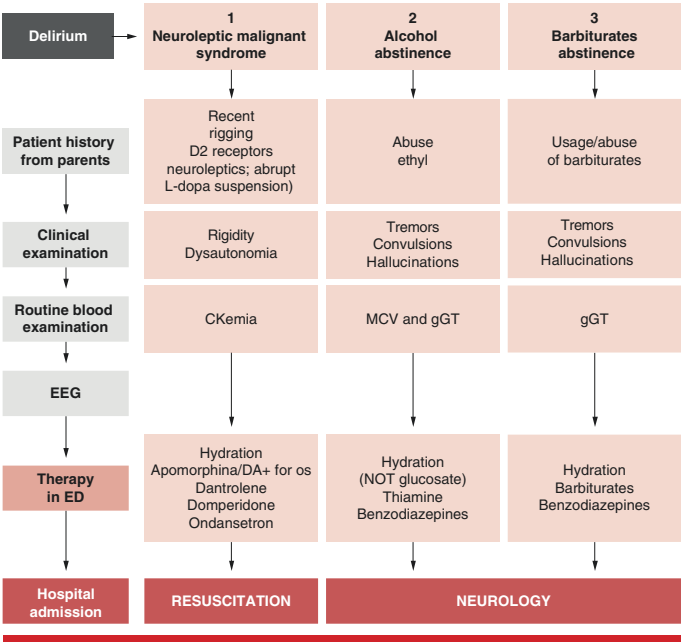


Figure 6.3 **Diagnostic-therapeutic protocol in conditions associated with fever and delirium**



In the general scenario we have also considered a miscellany of other **neurological emergencies that come into differential diagnosis** with the previous ones because, although they are not inflammatory in nature, they are often accompanied by fever, such as subarachnoid haemorrhage (SAH) and cerebral venous thrombosis (CVE). These are diseases which, from the nosological point of view, belong to the group of cerebrovascular diseases, but which, due to their inaugural characteristics, partially follow the diagnostic pathways of infectious/inflammatory diseases. For the management of these diseases, there are links within the algorithm that refer to specific paths (focal neurological deficits, epileptic manifestations, Chaps. 10 and 4) developed within the project.

Diagnostic Framework

For the diagnostic framework and the definition of the pathways of infectious/inflammatory diseases, we have used the evidence-based data available in the literature and derived from studies that we still have in progress. In the initial picture of the febrile patient we considered as symptoms that allow the orientation towards an infectious disease of the CNS **encephalopathy** (understood in a generic sense as a symptom of widespread dysfunction of brain structures) and **headache**, a very common symptom but unspecific.

Diagnosis in ED: Priority Goals

- Pre-aetiological detection of bacterial meningitis
- Catching the differences between a simple meningism and a meningoencephalopathy
- Identify these abstinential conditions:
 - ☐ Neuroleptics
 - ☐ L-dopa
 - ☐ Ethyl alcohol
 - ☐ Barbiturates

Synthetic Anamnestic Sheet: Main Questions to Ask

- Generals:
 - ☐ Duration of hyperthermia and/or headache
 - ☐ Time of onset of symptoms of encephalopathy
 - ☐ Accompanying systemic symptoms
 - ☐ Any causes of immunocompromising¹:

¹How do I change the scenario in case of immunocompromising? According to the data of the classical literature, we know that the most frequent meningoencephalitis in the immunocompetent patient (in our geographical area) are pneumococcal, meningococcal, HSV1, HSV2 and enterovirus. In the non-immunocompetent patient, in addition to the previous ones, encephalitis from HHV6, CMV, TB, listeria, toxoplasm, and Cryptococcus must be taken into consideration.

- HIV infection, history of solid or haematological tumours
- Recent transplants
- Immunosuppressive therapies
- Infectious:
 - Recent trips to other states or regions
 - Sting, arthropods and any associated skin marks
 - Recent contacts with infectious individuals
- Habits of life:
 - Alcohol abuse, barbiturates and benzodiazepines

History: Broad Spectrum of Initial Stage Variability

Meningism encephalopathy	Initial alteration of sensorium	Serious isolated
Feveret, rigor	Feveret, rigor	Fever, disturbance of the vigilance up to the coma
General malaise	Slight encephalopathy, headache	Epileptic seizures up to the status epilepticus, other focal or multifocal signs
<ul style="list-style-type: none"> • Enterovirus, EBV • Tuscany virus • Flu viruses • Seroconversion to HIV • NSAIDS 	<ul style="list-style-type: none"> • Mushrooms • Meningeal carcinomatosis • Systemic vasculitis 	<ul style="list-style-type: none"> • Bacteria, HSV, VzV • ADEM • Metabolic encephalopathies, abstinential encephalopathies, malignant neuroleptic syndrome • Primary cerebral vasculitis

CSF Examination

A fundamental point is the acquisition within a few hours of the CSF data, which often allows a more precise diagnostic orientation. The need to provide the pre-aetiological diagnosis as soon as possible requires the execution of the **lumbar puncture within the first 2 h** of medical observation. The examination should be preceded by a brain scan, but if this is not readily available and if there are no clear clinical signs of intracranial hypertension, the lumbar puncture should still be performed.

Table 6.1 Different CSF profile according to eziopathogenesis

Parameter (normal)	Bacterial	Viral	Multiple sclerosis	Mushroom	Autoimmune/postinfectious
Opening pressure (<170 mm)	>300	200	<200	300	200
WBC (<5)	>1000	<1000	<5	<500	<200
% PMNs (0)	>80%	1–50%	0	1–50%	0
Glucose (>40)	<40	>40	>40	<40	>40
Protein (<50)	>200	<200	<30	>200	<200
Gram stain (–)	+	–	–	–	–
Oligoclonal banding (–)	–	+/-	++	–	-/+

Modified from Somand and Meurer [7] and Marchioni et al. [8, 9]

Table 6.1 shows the main characteristics of the CSF profile under the various infectious/inflammatory conditions of the CNS. In particular, we point out the importance of neutrophilic pleiocytosis as an almost pathognomonic diagnostic criterion of bacterial meningitis.

Diagnostic and Therapeutic Priorities

Diagnostic Priorities [10–12]

Immediate measures (within 120 min)	Levels of evidence
Accurate history, routine, CPK, ammonia	
Cultures: at least three blood cultures for bacteria and fungi	D
Serology: <i>Listeria</i> , <i>Borrelia</i> b., HIV, HCV	B, II
Brain CT (if available within the time window)	
Lumbar puncture (physico-chemical, PCR for HSV1/2, VzV, enterovirus, CMV)	A, II/ A, I

Within 24–48 h	Levels of evidence
MRI brain, medulla, roots	B, II
EEGram: if you have any doubts about 'organicity', seizure or impossibility to carry out CT/LP immediately	C, III
Auto-antibodies screening	
Over 48 h	Levels of evidence
Anti-AQP4 antibodies: whether myelopathy with or without NORB	
Anti-GQ1b: if <i>brainstem encephalitis</i>	
Antibodies to SNC: whether limbic encephalitis or encephalomyelitis-radculitis	
Antibodies to potassium channel antibodies: if limbic encephalitis	
Multimodal evoked potentials	
EMG/ENG: if associated peripheral component	
Cerebral biopsy	C, III

Therapeutic Priorities [13, 14]

Within 2 h: bacterial hypothesis	Levels of evidence
Empirical antibiotics with good penetration into the CNS	D, GPP
Steroids and NSAIDs to reduce sequelae of bacterial lysis that is a cause of mortality (reduce the inflammatory process in the subarachnoid space)	A, (pneumococcus)
Within 10 h: viral hypothesis	Levels of evidence
Acyclovir	A, II
Medium Dose Steroids	D, GPP
Within 10 h: abstintential hypothesis	
Hydration	
Vitamin therapy, receptor therapy, sedative therapy, muscle relaxant therapy in relation to the type of abstinence: thiamine, benzodiazepines, barbiturates, D2 receptor agonists, baclofen therapy	
Within 24 h: autoimmune hypothesis	Levels of evidence
High-dose steroids/IV Ig	D, GPP

Diagnostic Procedures Based on the Clinical Scenario

In the development of the algorithm, the basic historical and clinical data that must be investigated are then considered. **Three distinct clinical scenarios** are subsequently developed (Figs. 6.4, 6.5, 6.6 and 6.7):

Figure 6.4 Initial classification and division into clinical scenarios

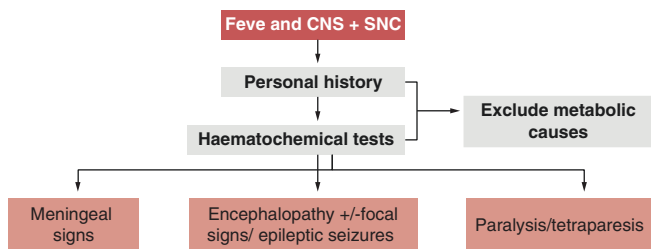


Figure 6.5 The patient with meningeal signs

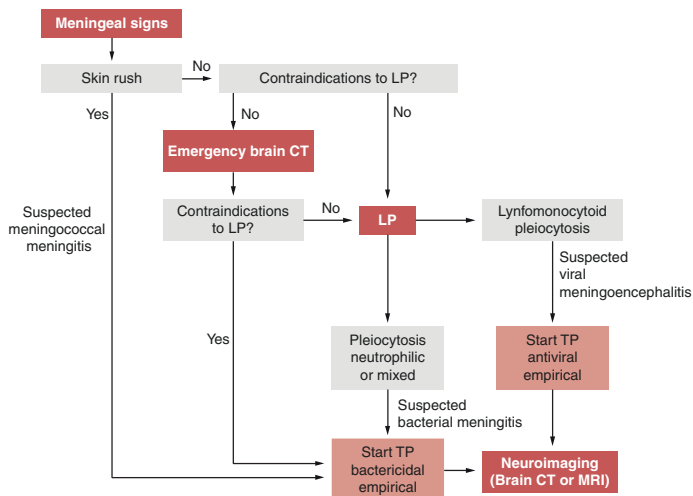
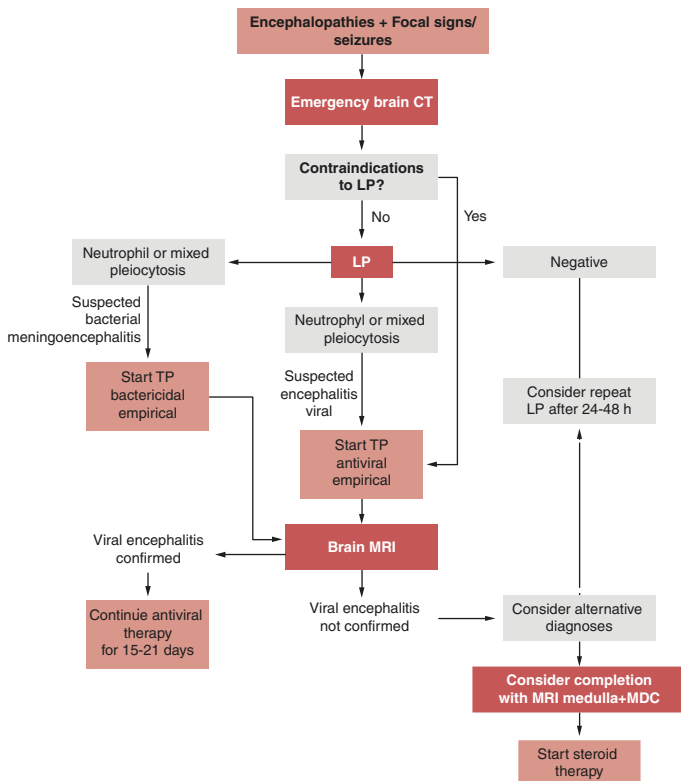
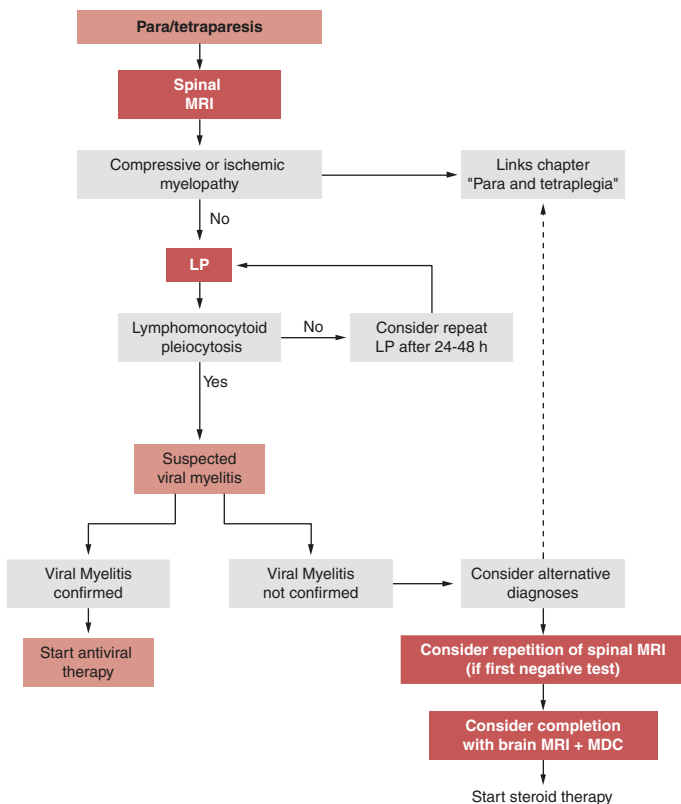


Figure 6.6 The patient with focal signs or seizures



- A scenario dominated by signs of meningeal impairment in the absence of focal signs, where the diagnostic priority is the early identification of bacterial meningitis
- A scenario in which the presence of focal signs or epileptic seizures raises the suspicion of the presence of a lesion occupying the brain space
- A scenario in which the symptomatology recalls an involvement of the spinal cord (para/tetraparesis)

Figure 6.7 Patient with para-/tetraparesis



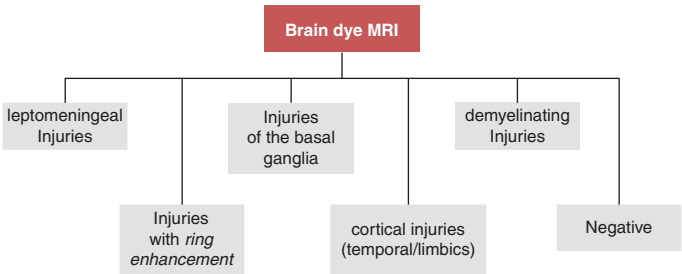
The key node of the first two procedures is the timing with which brain CT and lumbar puncture are performed. The lumbar puncture in particular becomes a priority examination in the suspicion of diseases such as bacterial meningitis, in which the delay in diagnosis of even a few hours is associated with a significant increase in mortality. The last scenario, on the other hand, aims at framing the medullary forms, which are rarely directly attributable to infectious causes [7, 15, 16].

See also Chap. 11.

Interpretation of Brain MRI patterns

Although brain MRI is not an examination normally performed as a matter of urgency, it is often a fundamental tool in defining clinical orientation and, in patients with fever and involvement of the central nervous system, should be acquired in early diagnostic stages of hospitalisation in the ward. Below we propose a schematic division into five lesional patterns, suggesting the possible related differential diagnoses (Fig. 6.8, Tables 6.2, 6.3, 6.4, 6.5 and 6.6) [17]. This tool is in no way intended to be exhaustive in defining the large number of diagnostic alternatives nor in defining the subsequent therapeutic process. However, we believe that it can be an easy reference tool for a first orientation in a pathological field as vast and complex as infectious/inflammatory diseases of the nervous system.

Figure 6.8 **Brain MRI lesional patterns in infectious/inflammatory diseases of the central nervous system**



Modified by: Aiken¹⁰

Table 6.2 Differential diagnosis in patients with leptomeningeal lesions

Leptomeningeal lesions			
Immunocompetent		Immunocompromised	
Differential diagnosis	Additional tests	Differential diagnosis	Additional tests
Bacterial/viral meningitis		Tubercular meningitis	Ziehl Neelsen, PCR for mycobacteria, culture for mycobacteria
Sarcoidosis	ACE on serum, high definition chest CT, PET total body		
Lymphoma localisation	Cytology and cytofluorimetry on CSF cells, PET total body	Lymphoma localisation	Cytology and cytofluorimetry on CSF cells, PET total body
Meningeal carcinomatosis	Cytological and cytospin on CSF cells		

Table 6.3 Differential diagnosis in patients with *ring-enhanced* lesions

Lesions with ring enhancement			
Immunocompetent		Immunocompromised	
Differential diagnosis	Additional tests	Differential diagnosis	Additional tests
Brain abscess		Tuberculoma	Ziehl Neelsen PCR for mycobacteria, culture for mycobacteria
Neurocysticercosis	Serology for <i>T. solium</i> on serum and liquor	Aspergilloma	Galactomannan on liquor
ADEM/PINS	Completion with medullary MRI; considers EMG/ENG to evaluate peripheral involvement; Ab anti-MOG	Primary CNS lymphoma	Cytology and cytofluorimetry on CSF cells; PCR for EBV; PET total body; biopsy

Table 6.3 Continued

Immunocompetent		Immunocompromised	
Differential diagnosis	Additional tests	Differential diagnosis	Additional tests
Glial cerebral neoplasm (glioblastoma)	Cerebral biopsy	Toxoplasmosis	PCR for EBV serologies and PCR for <i>T. gondii</i>
Multiple sclerosis (atypical forms)	Completion with spinal MRI; check the presence of CSF Oligoclonal bands		

Table 6.4 Differential diagnosis in patient with basal ganglia lesions

Lesions of the base ganglia			
Immunocompetent		Immunocompromised	
Differential diagnosis	Additional tests	Differential diagnosis	Additional tests
Creutzfeldt-Jakob Disease	Tau and 14.3.3 in CSFs	Other viral encephalitis	Consider PCR for West Nile
Dysmetabolic/accumulation diseases		Cryptococcosis	Cryptococcal CSF antigen

Table 6.5 Differential diagnosis in patients with cortical lesions

Cortical lesions (temporal/limbics)			
Immunocompetent		Immunocompromised	
Differential diagnosis	Additional tests	Differential diagnosis	Additional tests
Herpetic encephalitis	Repeat PCR on CSF; consider antibody index CSF for Ab anti-HSV	Other viral encephalitis	Consider PCR for CMV, HHV6, West Nile
Autoimmune encephalitis (limbic and non-limbic)	Ab antigens onconeural (e.g., Hu, Yo) Ab antigens neuronal surface (e.g., NMDAR, CASPR2) PET total body	Posterior reversible encephalopathy syndrome (PRES)	

Continued

Table 6.5 Continued

Immunocompetent		Immunocompromised	
Differential diagnosis	Additional tests	Differential diagnosis	Additional tests
Posterior reversible encephalopathy syndrome (PRES)			

Table 6.6 Differential diagnosis in patients with white matter lesions

White matter lesions			
Immunocompetent		Immunocompromised	
Differential diagnosis	Additional tests	Differential diagnosis	Additional tests
ADEM/PINS	Completion of medullary MRI; consider EMG/ENG to evaluate peripheral involvement; Ab anti-MOG	Progressive Multifocal Leukoencephalopathy (PML)	PCR for JCV
Neuromyelitis optica spectrum disorder	Completion spinal MRI; Ab anti AQP4; Ab anti-MOG	Immune reconstitution inflammatory syndrome (IRIS)	
Cerebral lymphoma (primary and secondary)	Cytology and cytofluorimetry on CSF cells; PET total body	Cerebral lymphoma (primary and secondary)	Cytology and cytofluorimetry on CSF cells; PCR for EBV; PET total body
Multiple sclerosis	Completion of spinal MRI assesses the presence of CSF OCBs		
Posterior reversible encephalopathy syndrome (PRES)		Posterior reversible encephalopathy syndrome (PRES)	

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7. Acute Vision Disorders

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Introduction

The present decisional algorithms are aimed at the evaluation, diagnosis, and therapeutic management of patients with acute vision disorders, for instance, visual impairment, disorders of eye movements, and alteration of pupillary reflexes [1].

Acute vision loss can be due to eye and neurological diseases, ischemic, dysmetabolic, traumatic, inflammatory, neoplastic, toxic, and genetic.

Eye movement disorders can be caused by intracranial (supra and infratentorial), orbital, or neuromuscular pathologies.

The **pupillary reflexes impairment** should be distinguished primarily by the presence or absence of a disorder of consciousness.

The diagnostic workout of acute vision disorders is based on an accurate anamnesis and clinical evaluation, supported by instrumental ophthalmological and neurological tests.

The therapies vary according to the etiopathogenesis of the symptom, whose eventual resolution therefore requires a careful assessment.

Vision Loss [2]

Definition

Reduction or complete loss of monocular or binocular vision, with onset from hyperacute (within seconds-minutes) to subacute (within hours-days).

Etiology

A vision loss can be caused by numerous eye and neurological disorders (Table 7.1). The following are the most frequent causes of acute/subacute vision loss.

Table 7.1 Causes of visual loss**Inflammatory/infectious**

Optical neuritis
Neuroborreliosis (Lyme disease)
Infectious neuropathies
Posterior reversible encephalopathy
Ophthalmic herpes zoster

Vascular

TIA/stroke
Cerebral/retinal venous thrombosis
Intracranial aneurysm
Retinal arteritis
Temporal arteritis
Behçet's disease
Retinal artery occlusion
Vasculitis (SLE, Sjogren's syndrome)
Pituitary apoplexy

Dysmetabolic/deficiencies

Alcohol-smoking neuropathy
Vitamin B12 deficiency

Inherited

Hereditary optical atrophy
Leber hereditary neuropathy

Compressive/infiltrative

Optical carcinomatosis
Glaucoma
Expansive processes

Other

Paraneoplastic neuropathy
Uveitis
Keratitis
Drugs and toxic
Chemotherapy
Migraine with aura
Hysteria (hysterical blindness)
Sarcoidosis
Dysthyroid neuropathy
Spinal and cardiac surgery

Diagnosis

The primary objective in PS is to distinguish between ophthalmic and neurological causes of visual impairment.

A careful and targeted anamnestic collection is fundamental for a good diagnostic classification in PS, but it is not always sufficient (Table 7.2). Sometimes it is appropriate to ask for both neurological and ophthalmological advice and follow the patient in the next hours.

Visual Drop from Prechiasmatic Cause

The acquired alterations of the prechiasmatic optical pathways include a series of pathologies (inflammatory, vascular, neoplastic, traumatic, infectious, toxic, and genetic) that involve the retina and the optical nerves up to the chiasma. The resulting visual deficits can be acute (inflammatory or ischemic processes) or slowly progressive as in the case of slow-growing optic nerve tumors (low-grade gliomas, meningiomas), infiltrative-inflammatory processes, or aneurysms.

The visual disturbance is monocular, and the campimetric deficit is unilateral. In rare cases there may be simultaneous involvement of both eyes [3].

Visual Loss from Prechiasmatic Neurological Cause on Inflammatory Basis (Optic Neuritis) [4]

- Definition:
 - **Papillitis**: inflammation of the optic disc/optic nerve head.
 - **Retrobulbar Optic Neuritis (ON)**: inflammation of the optic nerve fibers downstream of the ocular globe.
- Epidemiology:
 - Incidence: 1–5 per 100,000 per year; prevalence: 115 per 100,000; age 20–50 years (average 30 years); higher incidence among women (women-men 1.8:1), among Caucasians, and in northern areas (genetic factors?).

Table 7.2 Anamnestic elements required for the classification of the acute visual disturbance

Characteristics of visual drop	<ul style="list-style-type: none"> • Immediate onset/hours/days • Transient/permanent • Monocular/binocular • With field deficits (total/partial, hemianoptic/altitudinal) • With pain/without pain • Pattern type (altitudinal, vertical) • Factors of triggering (position, thermal variations, sexual activity) • Presence of retinal claudication (presence after transient loss of vision and blurred vision in the eye after exposure to intense light)
History of eye diseases	<ul style="list-style-type: none"> • Refractive defects, keratitis, uveitis, opticopathies, glaucoma, maculopathies, etc.
Extraocular history	<ul style="list-style-type: none"> • Vascular risk factors • Positive personal history for carotid stenosis, atrial fibrillation, or other thromboembolic diseases • Headache • Use of medicines • Toxic exposure • Nutritional deficits • Drug use (e.g., cocaine) • Genetic factors (familiarity, or matrilineal heritage) • Brain masses occupying space (neoplasms, aneurysms, abscesses) • Infectious problems • Malignant hypertension, eclampsia • Hypotension • Migraine • Prolonged surgical interventions • Genetic factors (familiarity, or matrilineal heritage)

■ Etiology: Table 7.3.

■ Typical signs and symptoms [5]:

- Reduced visual acuity (<4/10 in 52% of cases, <3/10 in 48%, <1/10 in 38%), mainly unilateral in adults (70–80%), more often bilateral in children (60%) where a reversible viral cause is more frequent and is more often in the form of papillitis with macular star (edema and exudate deposition in the perimacular area along the course of nerve fibers, with radial aspect).

Table 7.3 Pathologies mainly associated with optic neuritis

Demyelinating diseases	Isolated optic neuritis, multiple sclerosis, Devic's optic neuromyelitis, disseminated acute encephalomyelitis (ADEM), anti-MOG syndrome
Bacterial or viral infections, post-vaccine reactions	Syphilis, meningitis, tuberculosis, Lyme disease, chickenpox, adenovirus, shingles, HIV, mononucleosis, influenza virus, measles, rubella, hepatitis A and B
Fungal and protozoal infections	Aspergillosis, histoplasmosis, rickettsiosis, toxoplasmosis
Paranasal sinus diseases and other infections	Sinusitis, dental abscesses, middle otitis, mastoiditis
Dysimmune vasculitis/syndromes	Giant cell arteritis, SLE, PAN, Behçet's disease, Sjogren's syndrome, antiphospholipid antibody syndrome, collagen diseases, isolated vasculitis, sarcoidosis

- ☐ Pain (frequent, in 90% of cases), typically endo-periocular, accentuated by the movement of the eyes, which can precede the visual loss of even a few hours or days.
- ☐ Field alterations: widespread in 50–70% of cases, paracentral/peripheral in 20–40%, only central in 10%.
- ☐ Pupillary alterations: pupillary asymmetry (if the optic neuritis is unilateral), Marcus Gunn pupil (inability to maintain contraction under prolonged light stimulus).
 - Dyschromatopsia: frequent (in 80–90% of cases).
- ☐ Reduced light sensitivity and/or altered contrast sensitivity: frequent (in 80–90% of cases).
- ☐ Ocular fundus:
 - Papillitis: edema and/or hyperemia of the optic nerve
 - Retrobulbar ON: optic nerve of normal appearance
- Therapy in inflammatory/dysimmune syndromes [6, 7]:
 - ☐ Methylprednisolone IV 1 g/day for 3–6 days
 - ☐ Dexamethasone IM 8 mg/day × 7 days, 4 mg × 4 days, and 2 mg × 3 days
 - ☐ Plasmapheresis or IV IGG in the case of “aggressive” forms that are not responsive to steroids

Visual Loss from Prechiasmatic Neurological Cause on Vascular Basis

Retinal TIA (Amaurosis Fugax: Transient Visual Darkening) [8]

- Definition: transient unilateral loss of vision due to temporary deficit of blood supply to the retina.
- Etiology: the most common cause is an arterio-arterial embolism starting from a localized plaque at the level of the internal carotid artery, especially in middle-aged subjects with known vascular risk factors; it may also be due to cardiogenic embolism, aortic arch, arteritis, or coagulation alterations. Transient loss of vision in the presence of neck pain, particularly in young subjects, should lead to suspicion of carotid dissection. Horton's arteritis is a cause to be considered in the case of transient visual loss, especially if associated with headache and often tortuosity of the temporal artery detected on the skin plane, which appears serpiginous with increased consistency and reddened. Transient visual loss may precede an ischemic arterial optic neuritis or other manifestations of the disease and must be investigated in order to set up prophylactic therapy that avoids permanent loss of vision in one or both eyes.
- Typical signs and symptoms:
 - Blurred or loss of vision (partial or total) in one eye
 - Absence of pain, except temporal headache in Horton's arteritis which may be associated with diplopia
 - Duration from a few seconds to a few minutes (the patient often comes to medical observation when the symptoms have already resolved)
- Therapy:
 - In all patients, the control of vascular risk factors through interventions with lifestyle changes and drugs is indicated.
 - Secondary prevention medical therapy varies according to the pathogenesis of the event:
 - In the presence of atherothrombotic disease antiaggregant treatment
 - In the presence of embolic heart disease, oral anticoagulant therapy

- In the presence of symptomatic carotid stenosis >50–70% [9, 10], assess the indication for thromboendarterectomy or stenting
- In the presence of pre-retinal venous thrombosis which most frequently is the result of chronic atherosclerotic disease, treating vascular risk factors; if a history of hematological or collagen disorders sends to specialist hematological or rheumatological examination
- In the presence of retinal vasospasm, therapy with calcium antagonist, in the absence of permanent thrombotic phenomenon
- In the presence of retinal arterial thrombosis, antiaggregant therapy, or calcium channel blocker therapy if arteriolar vasoconstriction in the absence of thrombotic phenomenon

Retinal Infarction

- Definition: prolonged or permanent unilateral loss of vision caused by occlusion of the central artery of the retina or its branches, resulting in retinal infarction.
- Etiology: the causes are the same as for retinal TIA. The embolic or multi-embolic cause is the most frequent, but in the case of retinal infarction, there is no spontaneous revascularization in a short time, and therefore there is necrosis of the retinal cells. The presence of vascular risk factors and the presence of a history of polyvascular disease (coronary arteries, renal arteries, and vessels of the lower limbs) must always be sought.
- Typical signs and symptoms:
 - ☐ Blurred (partial or global) monocular vision.
 - ☐ Absence of pain.
 - ☐ At a very early stage, the ocular fundus can be normal, only later it can be seen retinal ischemic edema and, in some cases, intra-arterial thrombus.
- Therapy:
 - ☐ Acute phase:
 - Ophthalmic treatments aimed at displacing the embolus by means of ocular massage, reducing intraocular pressure, improving retinal blood flow.

- Cases of retinal ischemia treated with systemic or intra-arterial thrombolysis are reported, but there is no data to demonstrate in a certain way the benefits of these treatments.
- Secondary prevention varies according to the pathogenesis of the event:
 - In the presence of atherothrombotic disease, antiaggregant treatment.
 - In the presence of emboligenous heart disease, oral anticoagulant therapy.
 - In the presence of symptomatic carotid stenosis >50–70%, assess the indication for thromboendarterectomy or stenting.
 - In all patients, the control of vascular risk factors through lifestyle changes, and medication is indicated.

Ischemic Optic Neuropathies

Optical ischemic neuropathies (OINs) [11] are divided into [12]:

- **Posterior** (*posterior ischemic optic neuropathy, PION*):
 - Affect the intracanalicular portion of the optic nerve
 - Are quite rare
 - Secondary to blood flow reduction by intraoperative hypotension, anemia, and Trendelenburg position
 - In subjects over 50 years of age can be caused by temporal arteritis
 - Classically occur in patients undergoing long-term abdominal/cardiothoracic/spinal surgery
 - Risk factor: positive history of atherosclerotic disease
- **Anterior** (*anterior ischemic optic neuropathy, AION*):
 - They hit the head of the optic nerve
 - Are the most common
 - Over 50 years of age in 90% of cases
 - Are divided into:
 - Non-arteritic form (NAION)
 - Arteritic form (AAION)

Non-arteritic Form (NAION)

- Definition: visual loss due to retrolaminar infarction of the optic nerve (posterior ciliary artery). The recovery of the sight is variable (46% improvement of the visus).
- Epidemiology [13]: age >50 years, no sex preference, and presence of vascular risk factors.
- Etiology and pathogenesis [14]:
 - Hypoperfusion or hypotension (especially at night)
 - Sleep apnea syndrome
 - Neck and heart surgery (bypass)
 - Drugs (sumatriptan, sildenafil, tadalafil, nasal decongestants, amiodarone, interferon)
 - Altered self-regulation
 - Venous insufficiency
 - Small, crowded optical discs *disk at risk* (sign to be found during diagnosis in the contralateral eye)
- Signs and symptoms [15]:
 - Acute reduction of central monocular vision (visual impairment variable with respect to the portion of the field of view affected) with variable visual acuity (generally the reduction is less severe with respect to the arterial form and neuritis)
 - Mainly in the morning upon awakening (50% 2 h after getting up)
 - Absence of pain
 - Infrequent recurrences in the same eye, more likely to affect the other eye months or years after the first event (>20%)
 - Color vision deficiency
 - Afferent pupillary defect (*relative afferent pupillary defect*, RAPD)
 - Campimetric defect generally at altitudinal level (less than 50% cases)
 - VEP conduction defect (if central vision is compromised); acute phase ophthalmoscopy: nuance of papillary margins of varying degrees from segmental (superior species) to a florid papillary edema with flame hemorrhages, associated with thinning of arterial vessels; once the edema is resolved, a picture of optic atrophy without excavation remains

- Therapy [16]:
 - Correction of risk factors
 - ASA (prevents contralateral eye involvement)
 - High-dose pentoxifylline

Arteritic Form (AAION)

- Definition: important and permanent visual impairment associated with headache and temporal artery swelling.
- Epidemiology [13]: age of onset on average 50 years more frequent in women than in men (2/1).
- Etiology and pathogenesis: typically caused by giant cell arteritis; it is a systemic granulomatous vasculitis of medium- and large-size arteries. It is crucial to promptly differentiate AAION from NAION, because the correct diagnosis of AAION allows to act promptly with the therapy avoiding the involvement of the other eye.
- Signs and symptoms:
 - Frequent prodromes: fever, fatigue, weight loss, anemia, thrombocytosis, headache, mandibular claudication, visual blurring, and rheumatic polymyalgia (NB. The non-arteritic form is usually not associated with these symptoms and signs).
 - Rarely involving the kidney, lung, and skin.
 - Acute unilateral reduction of the visus; rare simultaneous binocular involvement, but the second eye may be involved within a few days (7–8 days).
 - Occlusion of the central retinal artery and of the cilioretinal artery, oculo-ischemic syndrome and the presence of exudates with cotton; in 15% of cases diplopia is associated; arterial retinal occlusion and paralysis of the extrinsic musculature may also present as the only ophthalmic sign of giant cell arteritis and precede ischemic opticopathy.
 - Color vision deficiency.
 - Monocular campimetric deficit.
 - Choroidal filling defects.
 - Acute phase ophthalmoscopy: edema of the disc involving the entire papilla, pearly “pale edema” (unlike NAION there is no congestion of peripapillary capillaries); flame hemorrhages are present in more than 50% of cases. Search for signs of associated retinal pictures on examination of the ocular fund.

■ Therapy:

- Steroids: methylprednisolone 1 g die IV for 3–5 days and then continue with oral steroid therapy.

Diagnostic Workflow for Acute Visual Impairment of Pre-chiasmatic Nature

■ Immediate measures (within 120 min):

- Accurate history: monocular or binocular deficit, onset and duration times, field abnormalities, pain, other concomitant, or previous symptoms
- Neurological examination with assessment of the presence of other signs associated with reduced vision, pupil motility, ocular alignment, and visual field for comparison
- Ophthalmology examination with assessment of vision, color vision and contrast, ocular background, ocular tone, and local signs
- Echo color Doppler of the neck vessels (if suspected artery-arterial embolism or dissection)
- Brain CT (if brain disease is suspected)
- Electrocardiogram (if cardiogenic embolism is suspected)

■ Measures within 24–48 h:

- Neurological reassessment
- Ophthalmic reassessment
- VEP (in the suspicion of optic neuritis: increased latency of the cortical response P100; interocular difference of latency P100; reduced amplitude N75-P100; non-evocable response)
- Computerized campimetry
- OCT (useful in acute phase to differentiate cases of papilledema from cases of pseudo-papilledema, for the differential diagnosis between pathologies of the macula and the optic nerve, to identify “early” alterations of the layer of ganglion cells in demyelinating diseases)
- Blood tests with screening for vascular risk factors, thrombophilia, vasculitis, and arteritis (if AAION, VES >50–80 mm/s)

■ Measures over 48 h/in selected cases:

- Fluorescein-angiography (if suspected ocular pathology in differential diagnosis)

- Brain MRI (if suspected demyelinating pathology) and orbital MRI (if suspected infiltrative/compressive pathologies of the optic nerve)
- Anti-aquaporin 4 antibodies (if suspected optical neuromyelitis), anti-MOG antibodies
- Temporal artery biopsy (if suspected Horton's arteritis)
- RM-angiography, CT-angiography, or conventional angiography
- Transthoracic/transesophageal echocardiogram
- Prolonged monitoring of cardiac rhythm for paroxysmal atrial fibrillation research

See decisional algorithm in Fig. 7.1.

Visual Loss Due to Chiasmatic/Retro-Chiasmatic Causes (Fig. 7.2) [17, 18]

Binasal Hemianopsia

- Definition: Loss of vision in the nasal visual half-fields bilaterally
- Etiology: rare condition due to bilateral aneurysms of the internal carotid artery, chiasmatic infarctions, and optical-chiasmatic arachnoiditis

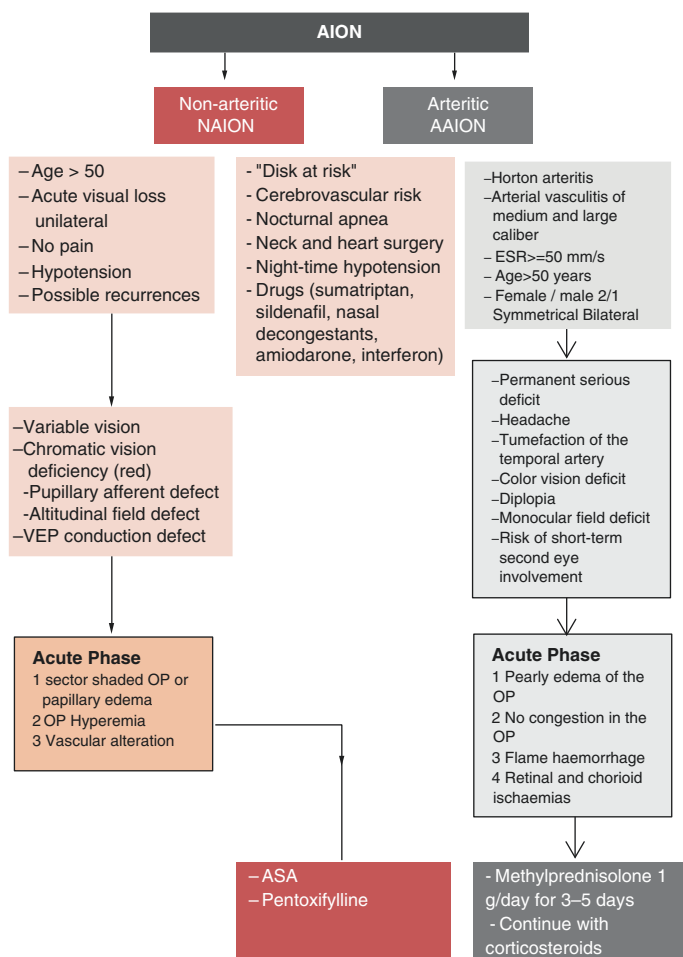
Two-Time Hemianopsia

- Definition: loss of vision in temporal visual half-fields bilaterally
- Etiology: compression of the optical chiasma by expansive processes of the sella (pituitary adenomas, colloid cysts, meningiomas, craniopharyngiomas, aneurysms, gliomas intrinsic to the chiasma)
- Signs and symptoms: the onset is generally gradual. It can be associated with headache and hormonal dysfunction

Homonymous Lateral Hemianopsia [19]

- Definition: loss of vision in the left or right hemispheres of both eyes. Sometimes the loss of vision can affect only the upper or lower portion of a half-field (quadrantanopsia).
- Etiology:
 - Main cause: vascular lesions more often ischemic (but also hemorrhagic) located in the territory of the anterior chori-

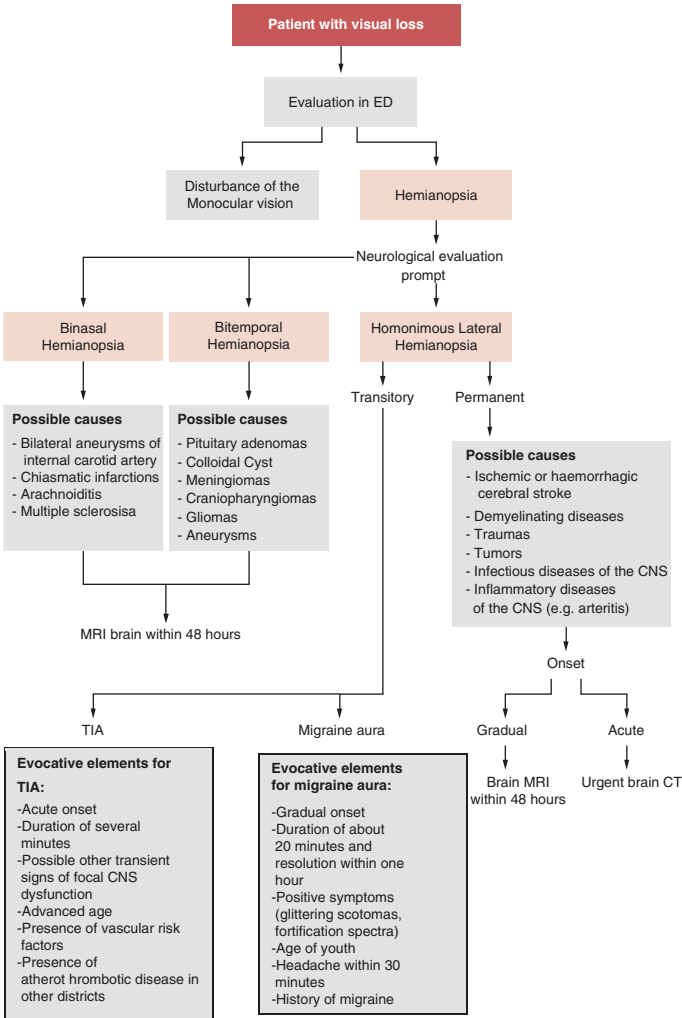
Figure 7.1 **Diagnostic-therapeutic algorithm of ischemic optical neuropathies**



dal artery (about 4% of all hemianopsias), or in the territory of the middle or posterior cerebral artery.

- Other causes: tumor processes, demyelinating disease, trauma, and arteritis.

Figure 7.2 Diagnostic framework of the hemianopsia symptom



- Signs and symptoms: there is rarely an isolated symptom, they associate:
 - If lesion at the level of the optical tracts or of the geniculated body: symptoms of involvement of the adjacent dien-

cephalic or mesencephalic structures (hemiplegia/paresis with hemihypoesthesia without aphasia); optokinetic nystagmus preserved.

- Whether lesions of optical radiation: disorder of strength, sensitivity, aphasia of Wernicke for lesions of the dominant hemisphere or neglect for lesions of the non-dominant hemisphere; optokinetic nystagmus absent from the side of the lesion and therefore contralateral to the hemianopsia. Often there are superior quadrantanopsia in the case of lesion of the temporal lobe optical radiation, inferior quadrantanopsia for lesions of the parietal lobe.
- If occipital lesions: hemianopsia clearly prevails with possible macular savings (central vision saved); behavioral disorders, and/or lack of awareness of the symptom may be associated.
- Bilateral primary visual cortex lesions: cortical blindness that may occur in patients with pre-existing hemianopsia when a lesion of the visual cortex is spared; they are generally of vascular origin, or in patients with abnormalities of the Willis polygon or in patients with self-regulatory deficit in case of malignant hypertension or PRES gravidarum eclampsia. If the hemianopsia is transient [20], suspect:
 - TIA, especially if: advanced age, acute onset, duration of several minutes, possible other transient signs of focal CNS dysfunction, presence of vascular risk factors, and presence of atherothrombotic disease in other districts.
 - Migraine with aura, especially if: juvenile age, gradual onset, duration of about 20 min and resolution within 1 h, positive symptoms (glittering scotomas, fortification spectra), headache within 30 min, and history of migraine.

Diagnostic Workup for Acute Visual Loss of a Chiasmatic/Retro-Chiasmatic Nature

- Immediate measures:
 - A thorough medical history
 - Neurological examination with evaluation of the presence of signs associated with loss of vision, pupil motility, ocular alignment, and visual field for comparison

- ☐ Ophthalmology examination with assessment of vision, color vision, and contrast, of the ocular background, of the ocular tone
- ☐ Computerized campimetry
- ☐ Brain CT
- Measures over 48 h:
 - ☐ Brain MRI
 - ☐ Angio-MRI of the intracranial vessels
 - ☐ Dosage of pituitary hormones (bitemporal hemianopsia)

Therapy for Acute Visual Impairment of a Chiasmatic/Retro-Chiasmatic Nature

The therapy, also in relation to acute management, must be targeted at the pathology responsible for the visual field deficit. For patients in whom it is caused by an acute cerebrovascular event the management should be as reported in the dedicated section.

Differential Diagnosis of Acute Visual Impairment (Figs. 7.3, 7.4, 7.5, and 7.6)

Figure 7.3 Differential diagnosis based on the age of the subject with visual impairment

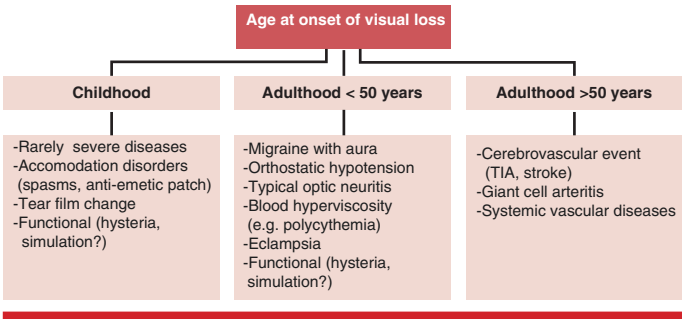


Figure 7.4 (a, b) Differential diagnostics based on the time of onset and persistence of visual impairment

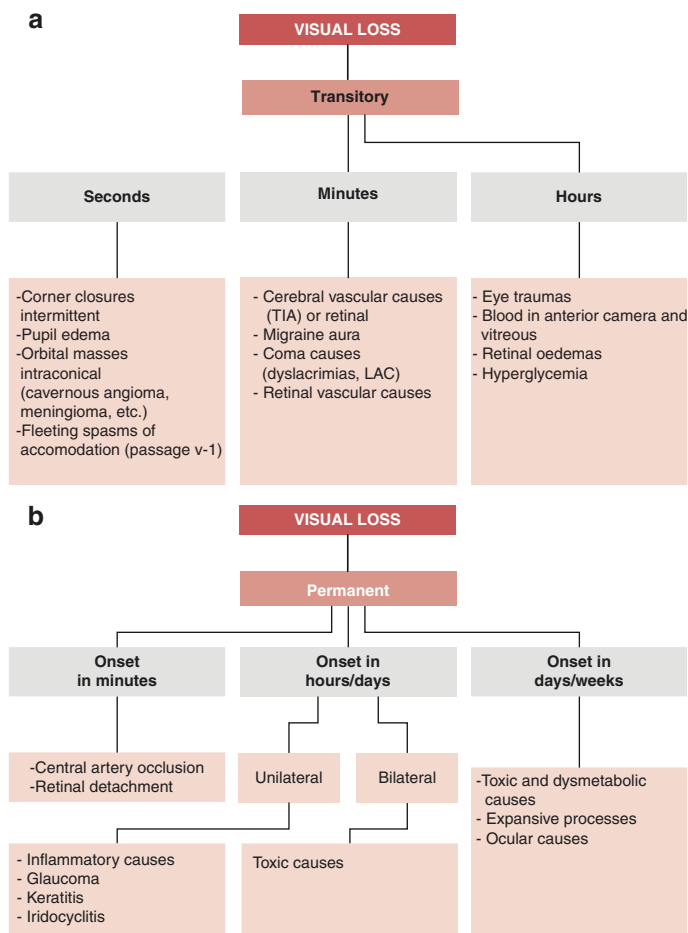


Figure 7.5 Differential diagnosis based on visual drop distribution (unilateral or bilateral)

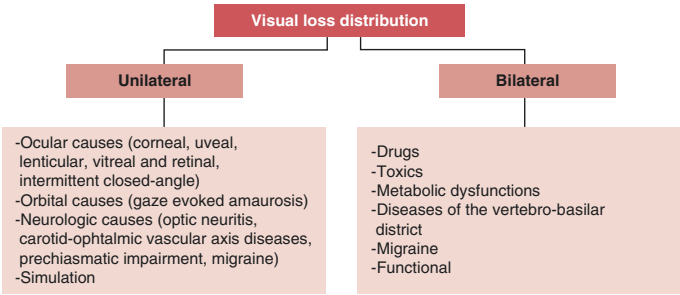
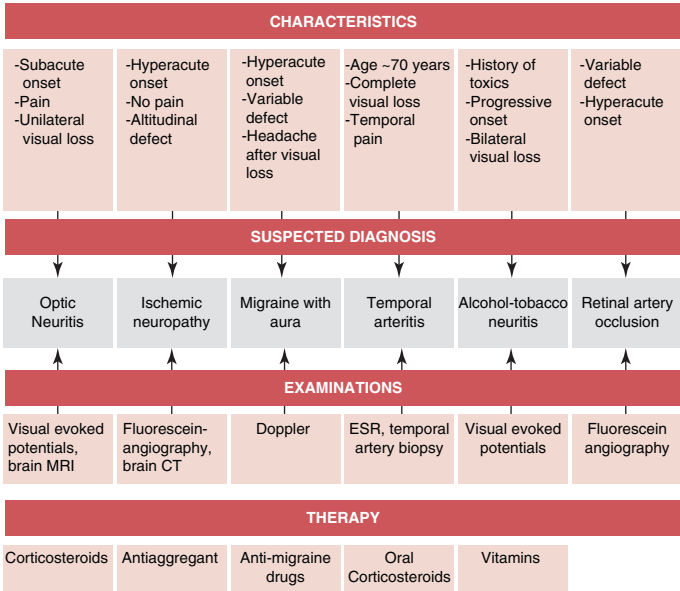


Figure 7.6 Clinical patterns typical of the most frequent causes of visual impairment, diagnostic procedure, and therapy



Extraocular Muscle Palsies [21]

Definition

Extraocular muscle palsy causes diplopia (double vision), which is always binocular (it disappears when one eye is closed). In turn, binocular diplopia can be episodic, intermittent, or continuous, and it should be assessed whether diplopia is accompanied by eyelid ptosis and pain.

Causes of Extraocular Muscle Palsies

The causes of extraocular muscle palsy can be of various kinds (vascular, expansive, inflammatory, dysmetabolic, neurodegenerative, neuromuscular). The ocular motor disorder does not always arise sharply; however, even a progressive disorder can subacutely worsen and lead the patient to the ER (Table 7.4). Furthermore, ophthalmoplegia may be accompanied by pain (Table 7.5) [22].

Semeiology of Acute Ophthalmoplegia

Diagnostic Procedures for Acute Ophthalmoplegia (Figs. 7.7 and 7.8)

■ **Immediate measures:**

- ☐ Accurate medical history, neurological examination, and laboratory routines
- ☐ Brain CT + angio-CT (suspected basilar artery thrombosis, cavernous sinus thrombosis, etc.)

■ **Measures within 24–48 h:**

- ☐ Contrast-enhanced brain CT or brain MRI with Angio-MRI
- ☐ Carotid and transcranial ultrasound
- ☐ Lumbar puncture (if suspected infection or polyradiculoneuropathy) for visual, microscopic and chemical CSF analysis, isoelectrofocusing, and polymerase chain reaction
- ☐ Angiography (if extrinsic/intrinsic paralysis and MRI not indicative)
- ☐ EMG

Table 7.4 Causes of acute and non-acute ophthalmoplegia

Causes of acute ophthalmoplegia	Causes of non-acute ophthalmoplegia
<i>Brain stem injuries</i>	
Midbrain or pontine infarction Multiple sclerosis Wernicke's encephalopathy	Progressive supranuclear palsy Oculo-pharyngeal muscular dystrophy Mitochondrial myopathies Myotonic dystrophy type 1 Expansive masses Graves ophthalmopathy Monofocal myositis
<i>Cranial nerve injury</i>	
Miller-Fisher Syndrome Cavernous sinus thrombosis Cranial mononeuropathy Paraneoplastic syndrome Infiltrative pathology of the skull base (Inflammatory-infective-carcinomatosis)	
<i>Neuromuscular junction disorders</i>	
Myasthenia Lambert-Eaton syndrome Botulism	

Table 7.5 Causes of painful ophthalmoplegia

Vascular
Intracavernous carotid aneurysm Posterior or communicating posterior cerebral artery aneurysm Cavernous sinus thrombosis Carotid-cavernous fistula Temporal arteritis Ophthalmoplegic headache
Neoplastic
Adenoma of the pituitary gland Pituitary apoplexy Pericavernous meningioma Cavernous sinus metastasis Orbital bone cancer Nasopharyngeal tumors with invasion of the cavernous sinus Meningeal carcinomatosis

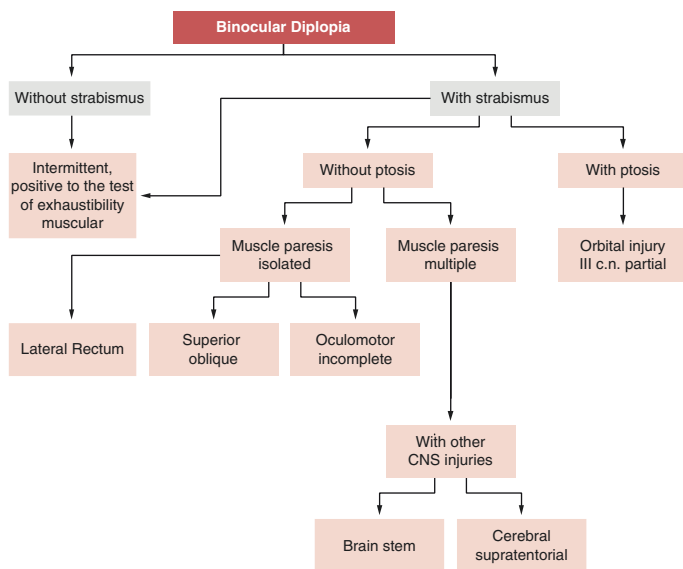
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Table 7.5 Continued

Inflammatory-infective

Tolosa-Hunt syndrome
 Orbital pseudotumor
 Sinusitis or mucocele
 Herpes zoster
 Sarcoidosis
 Mucormycosis

Figure 7.7 Clinical-diagnostic framework for acute ophthalmoplegia



☐ TSH, Ab anti-TSH receptor, Ab anti-Ach receptor, Ab anti-GQ1b

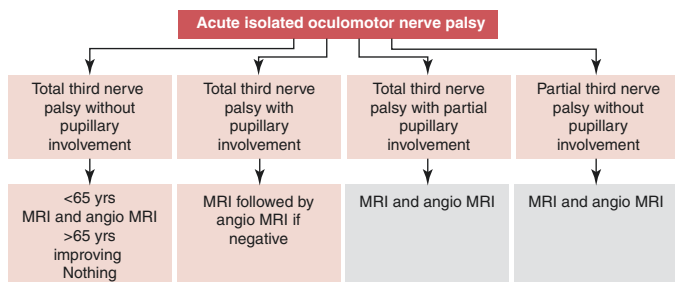
☐ Orbit MRI

■ **Measures over 48 h:**

☐ Genetic testing for myopathy

☐ Muscle biopsy

Figure 7.8 Diagnostic procedure in patients with isolated acute ocular-motor nerve paralysis



*Brain angiography is still recommended if: (1) the worsening of the extrinsic and intrinsic deficit continues beyond 14 days; (2) the intrinsic deficit progresses to an anisocoria >1 mm; (3) there is no improvement within 12 weeks; (4) signs of aberrant regeneration. Note—Consider performing a CSF analysis to rule out an inflammatory-infective-carcinomatous process.

Differential Diagnosis

Causes of Diplopia Usually Without Strabismus

■ **Myasthenia gravis.**

Characteristics: intermittent, reproducible with muscular exhaustion, serotonin ptosis, and pattern not related to central or peripheral lesion of one of the cranial nerves.

Diagnosis: EMG with repetitive motor nerve stimulation or single-fiber EMG (SFEMG), Ach receptor antibodies, and *ice-pack* test for ptosis.

Causes of Strabismus with Ptosis

■ **Retro-orbital injury:**

□ **Pathology of the cavernous sinus.** Cavernous sinus thrombosis, dural arteriovenous fistula, intracavernous carotid fistula, and intracavernous carotid aneurysm.

□ **Posterior communicating artery aneurysm.**

Characteristics: pulsating exophthalmos, pain, conjunctival hyperemia, and sensory deficit in trigeminal branch I territory. The pupil innervation is always involved.

Diagnostics: brain CT and angio-CT, brain MRI and angio-MRI, and angiography.

■ Orbital injury:

□ Intraorbital neoplasms.

Characteristics: slow course, pain, often eye proptosis, and conjunctival injection. Frequently parasellar meningiomas and infiltrating pituitary adenomas, sometimes lymphomas.
Diagnostics: brain and orbit CT and MRI.

□ Infectious inflammatory disease (mucormycosis).

Characteristics: subacute course (2–3 days), eyelid edema, exophthalmos or proptosis, and pain during eye movements/painful ophthalmoplegia. Fever, flu-like symptoms.
Diagnostics: orbit and paranasal sinus CT, ENT evaluation.

□ Pseudo-tumor orbit.

Characteristics: inflammatory-granulomatous process at the orbital level with inflammatory swelling of the extraocular muscles and other structures contained in the orbit. It is accompanied by conjunctival and palpebral injection and proptosis.
Diagnostics: orbit CT, ultrasound, and orbit MRI (to visualize the increase in volume of the orbit structures).

■ Peripheral pathology in subarachnoid space:

□ Posterior communicating artery aneurysm.

Characteristics: paralysis of the third cranial nerve with pupillary involvement at onset, pain. In almost all patients, there is a history of symptoms related to the involvement of the third cranial nerve before the rupture of the aneurysm.
Diagnostics: brain CT and angio-CT, brain MRI and angio-MRI, and angiography.

□ Meningitis, ischemia, tumors, endocranial hypertension, chronic subdural hematoma, and trauma.

Causes of Ptosis Without Strabismus and Isolated Muscle

Paresis [23–25]

■ Partial ocular motor palsy (III c.n.) with normal pupil [26] or

■ Trochlear nerve palsy (IV c.n.) or

■ Abducent nerve palsy (VI c.n.)

□ Diabetes.

Characteristics: development in a few hours, spared pupil if the central portion of the nerve is involved, sometimes pain, good prognosis.

Diagnostics: brain CT, hematochemical tests including glycated hemoglobin and glucose tolerance test.

❑ **Vascular disease.**

Characteristics: ophthalmoplegic migraine with *vasa nervorum* spasm; more rarely midbrain ischemic infarct or hemorrhage (often associated with other symptoms and signs of the CNS).

Diagnostics: brain CT and angio-CT or brain MRI and angio-MRI.

❑ **Dysthyroidism.**

Features: especially in hyperthyroidism (Graves' disease), often bilateral, edema of the inferior (the most involved among the extraocular muscles) and superior rectus muscles with important lymphocyte infiltrate.

Diagnostics: thyroid function indexes, antithyroid antibodies (especially anti-TSH receptor antibodies), orbit CT to detect increased volume of the eye muscles.

❑ **Trauma.**

Characteristics: skull base fractures, at the level of the *clivus*, at the level of the petrous apex (associated with trigeminal pain, Gradenigo's syndrome).

Diagnostics: brain CT with bone and orbit sequences.

❑ **Undetermined cause.**

Characteristics: often idiopathic, sometimes neurovascular compression phenomena by the circumflexed branch of the basilar artery.

Diagnostics: brain CT and angio-CT and brain MRI and angio-MRI.

❑ **Intracranial hypertension.** Paralysis of the VI c.n. due to a particular vulnerability of the nerve along its course and particularly at the level of the sphenoidal crest, before entering the cavernous sinus.

Characteristics: multiple causes, idiopathic (*pseudotumor cerebri*), neoplastic (especially metastatic tumor from the nasopharynx), and infectious (meningitis).

Diagnostics: contrast-enhanced brain CT and/or MRI, CSF analysis with measurement of the CSF pressure.

Causes of Strabismus Without Ptosis and Multiple Muscle Palsy [27]

■ With brainstem lesions:

□ Demyelinating disease.

Characteristics: often mixed paralysis of gaze and eye muscles; plaques located in the brainstem at the level of the oculomotor nerves nuclei; sometimes pontine plaques with damage to the pontine nuclei for gaze control and to the medial longitudinal fascicle of the same side [28].

Diagnostics: brain CT, contrast-enhanced brain MRI, CSF analysis with detection of oligoclonal bands.

□ Vascular disorder.

Characteristics: vertebrobasilar ischemic stroke or hemorrhage of the brainstem; sudden development; if located in the mesencephalic roof it is accompanied by paralysis of the vertical gaze (Parinaud's syndrome). Eye movement disorders can also be present in vascular disorders in the hemispheres, basal ganglia, and thalamus.

Diagnostics: brain CT with angio-CT and brain MRI with angio-MRI.

■ With brain lesions:

□ Cancer.

Characteristics: slow and progressive development, intracranial hypertension with headache and papilledema.

Diagnostics: contrast-enhanced brain CT or MRI.

□ Progressive supranuclear palsy.

Characteristics: slow and progressive course, supranuclear ophthalmoplegia with deficit of the vertical gaze, subsequent complete paralysis of gaze; association with axial dystonia and pseudobulbar paralysis.

Diagnostics: brain MRI (mesencephalic atrophy) and DAT scan.

□ Wernicke's encephalopathy.

Characteristics: association of ataxia, cognitive and eye movement disorders with paralysis of the external rectus muscle, often bilateral (in a suitable clinical context pathognomonic blockage of the horizontal gaze), frequent internuclear ophthalmoplegia.

Diagnostics: hematochemical tests including thiamine dosage and brain MRI (hypothalamic alterations).

■ **With palsy of muscles supplied by the cranial nerves:**

□ **Oculo-pharyngeal muscular dystrophy.**

Characteristics: autosomal-dominant transmission, adult onset, bilateral ptosis, ophthalmoparesis, and dysphagia.
Diagnostics: EMG, muscle biopsy (*rimmed vacuoles*), and genetic investigation (PABP2 gene, 14q11.1).

■ **With limb muscle weakness:**

□ **Mitochondrial myopathies.**

Characteristics: Kearns-Sayre syndrome in childhood or young adult or PEO syndrome in adult (clinical phenotype of multiple alterations of mitochondrial DNA that result in alterations of oxidative phosphorylation) characterized by ptosis, retinitis pigmentosa, and cardiac conduction disorders.

Diagnostics: muscle biopsy and genetics.

□ **Congenital dystrophies.**

Characteristics: heterogeneous group of rare perinatal onset diseases with slow progression, associated with brain anomalies due to alterations in neuronal migration due to a deficit of merosin or glycosylation (Walker-Warburg syndrome and muscle-eye-brain disease, with ocular alterations of various kinds).

Diagnostics: CPK and brain MRI (pachygyria, lissencephaly).

Causes of Internuclear Ophthalmoplegia [27]

Disturbance present in numerous syndromes of the brainstem characterized by paralysis of the horizontal gaze due to the lack of synergism between the medial rectum muscles of one side and lateral rectum muscles of the opposite side. It is due to the unilateral or bilateral lesion of the medial longitudinal fascicle.

■ **Unilateral**

□ **Vascular disorder.**

Characteristics: small paramedian pontine infarction and lateral bulbar infarction.

Diagnostics: Acute phase brain CT, brain MRI with angio-MRI.

□ **Demyelinating disease.**

Characteristics: demyelinating lesions at the pontine level; it's the most frequent cause of internuclear ophthalmoplegia.

Diagnostics: brain CT scan, contrast-enhanced brain MRI, and CSF analysis with search for oligoclonal bands.

□ **Neoplasms.**

Characteristics: tumors of the brainstem or the IV ventricle.

Diagnostics: contrast-enhanced brain CT or MRI.

□ **Other diseases** (e.g., SLE).

Characteristics: ischemic or demyelinating lesions of the brainstem.

Diagnostics: hematological tests (anti-nuclear antibodies, antiphospholipid antibodies) and cerebral MRI with angio.

■ **Bilateral**

□ **Demyelinating disease.**

Characteristics: demyelinating lesion in the posterior part of the central pontine tegment with lesion of both medial longitudinal fascicles.

Diagnostics: brain CT, contrast-enhanced brain MRI, and CSF analysis with search for oligoclonal bands.

□ **Pontine myelinolysis.**

Characteristics: demyelination area in the central part of the pontine base due to severe hydro-electrolytic imbalance of various genesis (m. of Addison, alcoholism, sepsis, etc.).

Diagnostics: brain CT, hematological tests (ionemia), and brain MRI.

□ **Vascular disorder.**

Characteristics: ischemic or hemorrhagic lesion in the posterior part of the central pontine tegment, often associated with other signs and symptoms of the CNS.

Diagnostics: brain CT and brain MRI.

□ **Other pathologies.** Wernicke's disease.

Characteristics: floor-level lesions of the IV ventricle with internuclear ophthalmoplegia and paralysis of the lateral rectus muscles; ataxia and cognitive disorders are associated.

Diagnostics: brain CT and hematological tests including thiamine dosage and brain MRI (hypothalamic alterations).

Causes of Vertical Diplopia (Skew Deviation)

Vertical ocular misalignment due to pre-nuclear lesion along the peripheral or central otolithic vestibular pathways (see Chap. 8) may be associated with ocular torsion towards the lower eye, head, and subjective visual vertical (ability to judge verticality in the absence of environmental references) tilt in the same direction (ocular tilt reaction, OTR).

■ Typical signs and symptoms:

- ☐ Slight or absent vertical diplopia.
- ☐ Vertigo.
- ☐ The ocular deviation typically does not vary in the different positions of gaze (comitant), thus differing from the ocular misalignment in the vertical plane due to paralysis of the eye elevator or depressor muscles.

■ Etiology:

- ☐ Wallenberg syndrome (lateral medullary vascular lesion with involvement of the vestibular nuclei, hypotrophy on the side of the lesion).
- ☐ Postero-medial cerebellar lesions (in the territory of the PICA).
- ☐ Vascular or demyelinating lesions along the medial longitudinal fascicle.
- ☐ Mesencephalic lesions involving the interstitial nucleus of Cajal.
- ☐ Acute peripheral vestibular syndrome.

■ Diagnostics:

- ☐ Neurological and neuro-otological examination.
- ☐ Brain MRI with study of intracranial vessels (when peripheral pathology has been excluded).

Neuro-Ophthalmological Changes in the Patient with Disorders of Consciousness

See also Chap. 2.

The evaluation of the pupils is extremely important, especially in patients with disorders of consciousness.

The first step in defining the cause related to asymmetry of pupil diameter [29] is the distinction between damage of the orthosympathetic pathway (greater anisocoria in the dark) and damage of the parasympathetic pathway (greater anisocoria in the light) (Fig. 7.9). The study of the pupillary reflex is also fundamental (Fig. 7.10).

The evaluation of pupillary reflexes completes the neuro-ophthalmological examination by providing useful information for the diagnosis of both an acute vision loss, often being altered

Figure 7.9 Anisocoria diagnostic flow chart

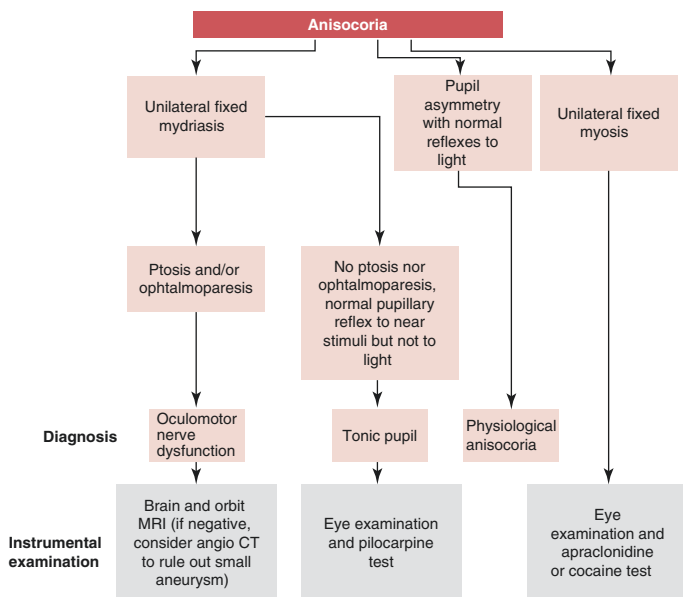


Figure 7.10 Differential diagnosis of coma based on pupil evaluation

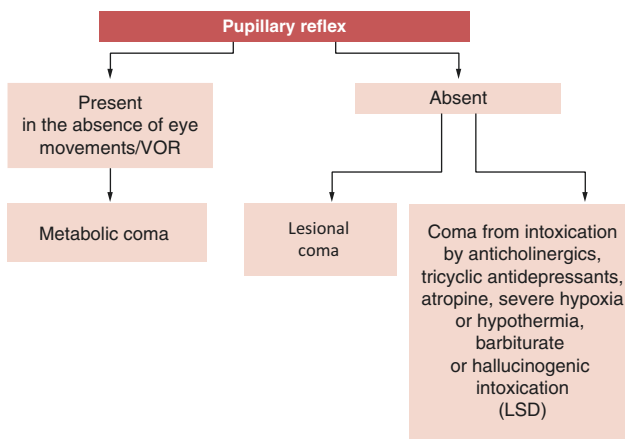


Figure 7.11 Possible lesion sites in Horner’s syndrome

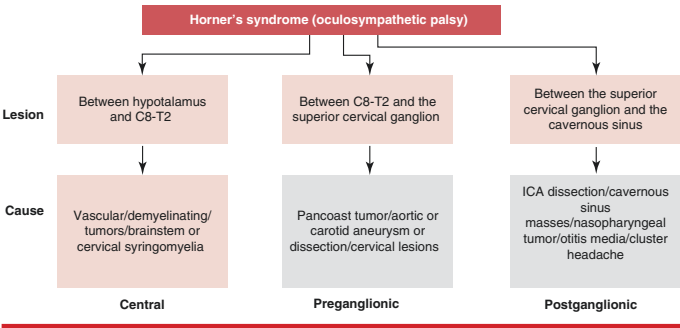


Table 7.6 Pupillary abnormalities and lesion localization in coma patients

Pupillary abnormalities	Lesion sites
Bernard Horner’s syndrome	Medulla or hypothalamus
Miotic pupils, unimpaired reflexes	Bilateral diencephalon
Pupils in midposition with unimpaired reflexes	Midbrain tegmen
Pupils in midposition with impaired reflexes	Midbrain
Pinpoint pupils with impaired reflexes	Pons
Fixed pupils in midposition	Pons-medulla (deep coma)

either in some optic neuropathies (optic neuritis and NAION), and in diplopia, where it indicates the integrity of the intrinsic function of the oculomotor nerve and can therefore contribute to the diagnosis of the site of the lesion.

Pupillary reflexes may give some hints in patients with a disorder of consciousness, in whom it may suggest possible lesional sites (Fig. 7.11, Table 7.6) and causes of the disorder (Table 7.7).

See also Chap. 2.

In addition, the evaluation of eyelid motility, corneal reflex (Table 7.8), and eye movements (Table 7.9) can provide useful indications on the origin of the disorder of consciousness [30, 31].

Table 7.7 Pupillary diameter and cause of consciousness disturbance

Pupillary diameter	Cause of disorder of consciousness
Small and reactive pupils	Metabolic coma
Miosis reversible with naloxone	Narcotics poisoning
Small and reactive pupils	Diencephalic lesion
Fixed and dilated pupil, unilaterally	Uncal hernia
Fixed pupils, hippus	Tectal injury
Midposition fixed pupils	Brain injury
Pinpoint pupils	Pontine lesion

Table 7.8 Eyelid motility evaluation

Eyelid motility	
Preservation of the blink reflex	Mild disorder of consciousness
Eye opening to stimuli	Light coma
Blink reflex impairment	Severe pontine lesion or peripheral injury
Closed eyes and absence of orbicular tone	Bilateral lesion on the VII c.n. or pontine lesion
Blepharospasm	Metabolic encephalopathy, cerebellar hemorrhage, psychological disorder
Doll eyelids	Slight metabolic encephalopathy/SAH
Spontaneous blink	Spared pontine reticular formation
Blink to an acoustic stimulus	Spared lower pons

Finally, the evaluation of reflex eye movements induced by rotating the head (oculocephalic or doll's eyes maneuver) should be part of the neuro-ophthalmological evaluation, because it can contribute to the differentiation between a brainstem vs a brain lesion as a cause of ocular deviation. The passive rotation of the head on the horizontal or vertical plane produces a contralateral movement of the eyes, which is due to stimulation of the semicircular canals and their central connections. It must not be tested in cases of cervical trauma. The absence of a doll's eye reflex suggests either a dorsal brainstem damage or a severe metabolic disorder, which may be reversible with proper treatment [28, 32, 33].

Table 7.9 Eye movements evaluation

Eye movements	
Lateral deviation of gaze	Ipsilateral brain lesion or contralateral pontine/cerebellar lesions
Intermittent contralateral deviation	Frontal irritative lesion
Vertical tonic deviation	Hypoxic-ischemic encephalopathy
Vertical Strabismus	IV c.n. Paralysis
Slow horizontal pendular movements	Metabolic coma or brain lesion
Ocular bobbing (fast movement downward with slow return)	Pontine injury
Reverse ocular bobbing	Anoxic metabolic coma
Opsoclonus (fast conjugated movements in all directions)	Brainstem and cerebellar lesions

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8. Dizziness and Vertigo

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Maurizio Versino, and Maurizio Paciaroni

Introduction

Dizziness represents 10–15% of the causes of access to emergency and acceptance departments (on NEU Day 2018, the figure was 8%, with CI from 6% to 10%). The differential diagnosis of the patient

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with vertigo is of great importance in emergency department evaluation: similar clinical presentations can be supported by very different causes (otological, neurological, or systemic) with very different prognoses, and, on the other hand, the same pathology can correspond to different syndromes.

One of the main problems facing the patient with recent onset vertigo (minutes, hours) is the differential diagnosis between the various causes of vertigo and above all the determination of whether the symptoms can be traced back to an ischemic cerebral event, therefore liable to treatment in its acute phase. The problem arises when facing patient with isolated vertigo because when other neurological signs or symptoms are present the hypothesis of a central type disorder (possibly acute ischemic) appears simpler.

In the study of Lee and colleagues, out of 240 consecutive patients with isolated cerebellar infarction in the territory of cerebellar arteries diagnosed with magnetic resonance imaging (MRI), 25 patients (10.4%) presented in the acute phase only with isolated vertigo, suggesting vestibular neuronitis [1]. The posterior-inferior cerebellar artery (PICA) territory was the one most frequently affected in these cases (24/25: 96%), followed by the anterior-inferior cerebellar artery (AICA) territory (1/25: 4%). None of the patients had an infarct in the territory of the superior cerebellar artery (SCA).

A recent study has shown that the use of MRI in patients presenting for acute vestibular syndrome in the emergency room does not fully answer the question, as the DWI sequences used in the acute phase do not detect ischemic lesions in the posterior cranial fossa in up to 50% of cases [2].

The fact that vertigo in the emergency room is a major problem has recently been highlighted by a retrospective population study conducted on more than 40,000 patients who were discharged with a diagnosis of peripheral vertigo [3]. In a small percentage of them (0.18%), a stroke was then diagnosed within 30 days of discharge; although low, this percentage was about seven times higher than that of a control group. The authors' conclusions stressed, in

addition to the low incidence of the phenomenon, the fact that some strokes may be misdiagnosed as peripheral vertigo or that vertigo episodes may be warning signs of stroke [3]. The work was accompanied by an editorial where the following three considerations of public interest were highlighted:

- How big the problem of misdiagnosed stroke is in patients with dizziness
- If the causes of the misdiagnosis can be remedied
- Whether earlier correct diagnosis can improve stroke outcomes [4]

Clinical Criteria for Differential Diagnosis Between Vertigo of Peripheral or Central Origin

In acute vestibular deficits that occur with “isolated” vertigo (in the absence of other neurological signs), the symptoms and, above all [5], neuro-otological signs can point to a diagnosis of the site of the lesion, whether it would be affecting the peripheral or central vestibular system.

A recent review [6] reports the prevalence of vertigo and dizziness syndromes in 23,915 patients of the German Center for Vertigo and Balance Disorders in Munich and indicates a prevalence of central vertigo above 50%.

Peripheral vestibular syndrome is caused by a lesion affecting the vestibular component of the inner ear or the vestibular nerve along its course outside the brainstem. Vertigo is, in most cases, an illusion of movement of the visual scene (*external vertigo*); it is very intense, with associated neurovegetative phenomena. Vestibulo-spinal signs with a tendency to fall ipsilesionally may be associated. In the case of Ménière’s syndrome, auditory symptoms such as mild hearing loss, tinnitus, or fullness may be present.

- **Clinical findings** in a peripheral vestibular syndrome (e.g., right vestibular damage) in the acute phase:
 - Horizontal-torsional nystagmus beating (fast phase direction) to the left, more intense when the patient looks to the left and when fixation is removed (always present)

- ❑ Head impulse test positive when the head is turned to the right (always present)
- ❑ Head shaking test positive with nystagmus reinforcement (frequent)
- ❑ Ocular tilt reaction to the right (infrequent)
- ❑ Posture and gait unsteadiness with a tendency to lean to the right while standing (*Romberg test*) and walking with the eyes closed (no specificity and sensitivity data available)

If the patient is asked to walk back and forth with the eyes closed, the walking path will be star-shaped; if the patient is asked to walk 50 steps on the spot with the eyes closed (*Unterberger test*), he will turn to the right (no specificity and sensitivity data available).

The peripheral vestibular syndrome is typically characterized by nystagmus directed towards the healthy side. An exception may be found in the very early stages of the endolymphatic hydrops of Ménière's disease [7], when nystagmus can be directed towards the side affected by the pathogenic process.

Central vestibular syndrome is due to an injury that affects the fibers of the vestibular nerve in the brainstem, the vestibular nuclei, the projections from the vestibular nuclei, and the cerebellum. In the rare case in which the lesion only affects the intra-axial part of the vestibular nerve at the root-entry zone, although the location should be considered central, symptoms and signs will be the one described in the peripheral case. In the other cases, vertigo is, in most cases, less intense and may be an illusion of self-movement (*Internal vertigo*), the nystagmus is not horizontal-torsional (it can be purely horizontal, torsional, vertical, pendular), and its direction can change with the direction of gaze. On Romberg's maneuver, the patient shows a tendency to fall in a variable direction; the gait and indexes tests may or may not show veering in multiple directions and not necessarily in the opposite direction to the direction of the nystagmus. Other focal neurological signs, marked hypoacusia (for ischemic stroke in the

AICA territory, from which the internal auditory artery originates), and/or headache (either for lesions of the central nervous system or in the case of vestibular migraine) may be present.

Unfortunately, there is not a single sign or symptom that allows us to make a diagnosis of central or peripheral vertigo with certainty, but three clinical tests (head impulse test, nystagmus, skew deviation—HINT associated or not with hypoacusia—HINTplus), when used for the differential diagnosis of acute vestibular syndrome in patients presenting with a first episode of isolated vertigo, have demonstrated a sensitivity and specificity for vascular vertigo that is superior to acute phase brain MRI [8]. Performing these tests in patients entering the emergency room for an acute vestibular deficit has proven to be effective both in improving the correctness of the diagnosis and in reducing the costs associated with neuroimaging [9]. The following is an algorithm for the management of the patient with vertigo in the emergency room aimed at identifying cases with suspected central vertigo for whom neuroimaging should be performed with a delay that depends on the acuteness of the symptoms.

Proposal for a Diagnostic Algorithm for Vertigo in the Emergency Room

Definitions

When the patient complains of a generic sensation of “dizziness,” of “vertigo,” and of “unsteadiness,” one should distinguish between the following conditions:

- Vertigo
- Dizziness
- Unsteadiness
- Pre-syncope

Vertigo is defined as a “sensation of self-motion when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement” [10]. It is an illusion of movement, characterized by a sense of rotation or translation, and

can be referred to oneself (*internal vertigo*) or to the surrounding environment (*external vertigo*).

Dizziness is defined as “the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion” [10].

Unsteadiness is defined as “the feeling of being unstable while seated, standing, or walking” [10].

Pre-syncope is a feeling of impending loss of consciousness usually due to an overall reduction in cerebral blood flow. The most common causes are cardiovascular disorders, autonomic neuropathies, hyperventilation, postural hypotension, and vasovagal reactions. Carotid sinus hypersensitivity, leading to vasodepression and cardioinhibition, is the most important cause of pre-syncope in the elderly, often associated with falls.

Below are conditions that may give rise to pre-syncope and must therefore be investigated and sought in that case.

For differential diagnosis of pre-syncope conditions and pathologies such as:

- Symptomatic hypotension
- Hypertensive encephalopathy
- Arrhythmias
- Anemia
- Hypoxia
- Metabolic alterations
- Electrolytic alterations
- Hypo-/hyperglycemia
- Kidney failure
- Psychiatric disorders
- Side effects and intoxications from alcohol or drugs (e.g., anti-epileptics, tricyclic antidepressants, baclofen, dantrolene, tizanidine, orphenadrine, etc.)
- Neuropathies
- Chronic vascular encephalopathy

History Taking and First Evaluation of Vertigo

With a patient with vertigo, five elements must be acquired to build the case history through the “procedure” or “algorithm” developed by Belal and Glorig [11]:

- The timing (acute presentation or chronic symptoms)
- The coexistence of neurological symptoms and signs associated with vertigo
- The coexistence of audiological symptoms and signs
- The triggering, particularly with head movements
- The temporal pattern

The analysis of these elements contributes to the formulation of a differential diagnosis between **peripheral** or **central** vertigo. Table 8.1 for a list of causes of vertigo, whether acute, subacute, or chronic.

Figure 8.1 shows a series of consecutive actions which are illustrated below. In the final part of this chapter, the algorithm is reported.

With regard to neuroimaging, this should be interpreted essentially as MRI and/or angio-CT of neck and intracranial vessels.

Neurological Examination in the Patient with Vertigo

In all patients with acute vertigo, the presence of hearing loss (especially if sudden and unilateral) should be assessed, and a neurological examination should be conducted, according to the following checklist:

- Motor deficits
- Sensory deficits (proprioceptive, tactile-painful, but also thermal)
- Cerebellar signs: finger tests, dysarthria, stance, and gait
- Language disorders (aphasia)
- Oculomotor deficit (ocular alignment, saccadic, and smooth pursuit eye movements).

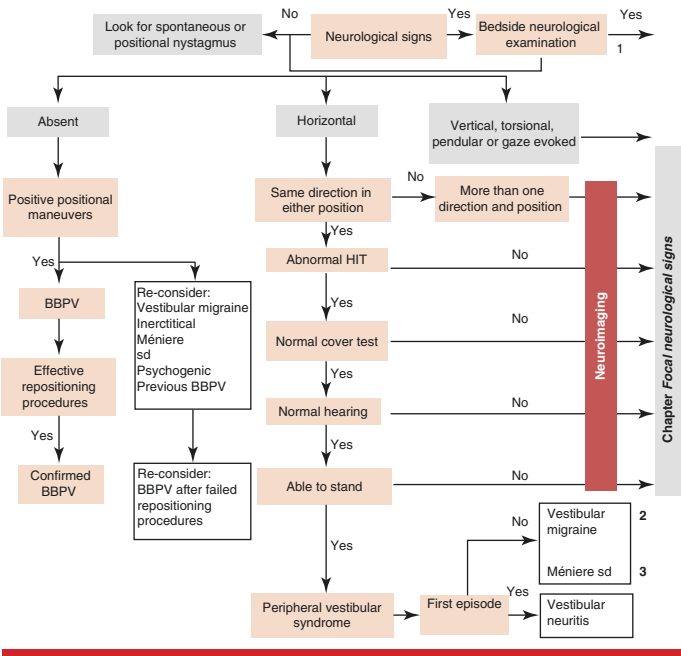
Table 8.1 Causes of vertigo (acute or subacute or chronic onset)

Causes	Description
<i>Peripheral causes</i>	
Acute labyrinthitis	Viral or bacterial infection of the labyrinth
Acute vestibular neuronitis	Viral or bacterial infection of the vestibular nerve (mostly from viral infection, as in the case of <i>herpes zoster oticus</i>)
Benign paroxysmal positional vertigo (BPPV)	Transient episodes of vertigo caused by stimulation of the vestibule due to canalolithiasis
Cholesteatoma	Cystic-like lesion often located in the middle ear and mastoid
Ménière's disease (Ménière syndrome; endolymphatic hydrops)	Recurrent episodes of vertigo, hypoacusia, tinnitus, or fullness caused by increased volume of the endolymph in the semicircular canals
Otosclerosis	Thickening and hardening of the tympanic membrane due to age or recurrent ear infections
Perilymphatic Fistula	Breaks between the middle and inner ear often due to trauma or excessive strain
<i>Central causes</i>	
Pontocerebellar angle tumors	Schwannoma (acoustic neuroma), subtentorial ependymoma, brainstem glioma, medulloblastoma, neurofibromatosis
Vascular causes (TIA, stroke)	Vertebrobasilar TIA, cerebellar stroke
Migraine	Vestibular migraine, basilar migraine
Multiple sclerosis	

- Deficit of cranial nerves (dysarthria and/or dysphagia, examination of the IX cranial nerve)
- Bernard-Horner syndrome
- Visual field deficits (test for comparison)
- Plantar reflex

In the case of acute vertigo, the detection of new onset neurological signs is indicative for a central cause.

Figure 8.1 **Algorithm for the diagnosis of vertigo in the emergency room**



Nystagmus (Table 8.2)

Nystagmus [12–19] is an involuntary eye movement that consists of two movements (phases) with opposite direction: a slow phase followed by a rapid phase, i.e., a saccade. The pendular nystagmus is the only form in which there is no rapid phase but rather two slow phases of opposite direction.

A nystagmus with a rapid and a slow phase is called a jerk nystagmus. The direction of the nystagmus (horizontal, vertical) is named by the direction of the rapid phase. In the torsional nystagmus instead the eye rotates in the frontal plane.

Table 8.2 Clinical aspects and most likely sites of injury in different types of nystagmus

Nystagmus	Clinical aspects	Injury site
Peripheral nystagmus	Horizontal-torsional nystagmus, always beating towards the healthy side	Vestibular nucleus, nerve, or labyrinth
Gaze evoked nystagmus	Present only in eccentric gaze, beats in the direction of gaze	Cerebellum (flocculus)
Downbeating nystagmus	Beating downward, particularly noticeable in lateral and downward gaze	Brainstem or cerebellum (flocculus)
Upbeating nystagmus	Beating upwards, particularly noticeable in upward gaze	Brainstem (paramedian medulla, pons, midbrain)
Pendular nystagmus	Slow phases (sinusoidal waveform) with horizontal, vertical, and torsional components leading to a circular or elliptical trajectory of the eyes	Brainstem
Periodical alternating nystagmus	Spontaneous, horizontal, reverses direction after a fixed period of time	Cerebellum (nodulus and uvula)

NB. There are no pathognomonic signs or symptoms of central or peripheral cause of vertigo

Nystagmus can be physiological when it occurs during prolonged rotation or while looking at a full-field moving image (optokinetic nystagmus), or it can be a pathological sign of vestibular or cerebellar damage.

Nystagmus should be evaluated in different eye position (gaze angle), both sitting and supine. It should also be assessed both with and without visual fixation. In case of peripheral nystagmus, the visuo-vestibular interaction can be used to attenuate the nystagmus (i.e., a nystagmus that attenuates when visual fixation is allowed is more likely to be peripheral).

Visual fixation can be prevented by using Frenzel's goggles, which consist of magnifying and backlit lenses. Alternatively, a

light source can be used to dazzle one eye and prevent fixation during observation by the operator, while the other eye is kept covered.

An additional method of preventing fixation while allowing the examiner to observe will be obtained by placing a blank sheet in front of the subject's eyes, covering the entire field of view.

Peripheral Vestibular Nystagmus

Peripheral vestibular nystagmus is caused by unilateral damage to the vestibular organ or vestibular nerve. However, a focal medullary lesion at the level of the vestibular nucleus or of the vestibular nerve fibers in the brainstem, at the level of the root-entry zone, causes a nystagmus with clinical characteristics of the peripheral type.

Peripheral nystagmus is more often a horizontal-torsional nystagmus, beating towards the healthy side, and is reduced or suppressed by visual fixation. The direction of the nystagmus does not change with the position of the eye in the orbit, but the amplitude and the speed of the nystagmus is increased by shifting gaze to the direction of the fast phase.

This is particularly true in the case of "continuous" vertigo. However, there are positional vertigo (i.e., triggered by changes in position) in which the peripheral nystagmus is vertical and torsional and changes direction in different positions.

In positional vertigo, nystagmus is not spontaneous but appears after certain movements, and in benign paroxysmal positional vertigo, it has typical characteristics. In the posterior semicircular canal variant, the Dix-Hallpike maneuver will elicit a vertical upbeating nystagmus with a torsional component, with reversal nystagmus returning to a sitting position (it becomes downbeating); in the lateral semicircular canal variant, the nystagmus is always positional but horizontal, geotropic (to the right on the right side and to the left on the left side), or apo-geotropic (to the left on the right side and to the right on the left side).

Gaze Evoked Nystagmus

The nystagmus evoked by the direction of the gaze is a nystagmus that is not seen in the primary position of gaze but only in the lateral gaze to the right or left, in the gaze up or down, and that beats in the direction of the gaze and changes direction depending on the direction of the gaze. It is independent of visual fixation and may be more evident in the supine position.

Vertical Nystagmus (Directed Upwards or Downwards)

The evidence of a vertical nystagmus (beating upwards or downwards) or of a purely torsional nystagmus should always suggest a central cause.

A downbeating nystagmus can be seen in all positions of gaze but is usually greater in lateral gaze. Convergence can increase it, inhibit it, or turn it into an upbeating nystagmus. Downbeating vertical nystagmus is not inhibited by fixation and is usually due to a dysfunction of the cerebellar flocculus.

The vertical upbeating nystagmus is usually greater in the upward gaze. It can be increased, inhibited, or transformed into a downward nystagmus by convergence. It is not inhibited by fixation. The lesion sites are the paramedian part of the medulla, the pons, and the midbrain.

Pendular Nystagmus

In the pendular nystagmus, there is not a rapid phase but only a slow back and forth movement. The direction can be purely horizontal or vertical, but it can also be a combination of the two or have other directions (e.g., diagonal). The oscillations can be conjugated (i.e., identical in both eyes), but more often they are different (greater in one eye). In some cases, pendular nystagmus may be monocular. In the acquired forms, the patient commonly reports oscillopsia.

An example of the above, with some video clips, can be found in Ref. [20].

Head Impulse Test (HIT)

The HIT is a bedside test. The examiner rotates the patient's head from a lateral position (alternately left and right) to a central position as quickly as possible, while the latter fixes a central target, such as the examiner's nose. HIT can also be done by rotating the head in the opposite direction, from the center to the periphery. The head should be turned only 10–15 degrees.

In the case of a normal vestibulo-ocular reflex during the rapid and passive rotation of the head, the eyes will move in the opposite direction to the rotation of the head in order to keep the gaze on the target; at the end of the movement of the head, the subject will not have to make any rapid movement of the eyes (saccade) to reposition the line of gaze on the target (HIT negative).

In the case of a defective vestibulo-ocular reflex, at the end of the head movement, the subject will perform a saccadic movement in the opposite direction to that of head rotation, in order to bring the line of sight back to the target (HIT positive).

In the case of a peripheral vestibular lesion, and therefore a peripheral vertigo, in the acute phase, the HIT will be positive for the rotations of the head towards the affected side and negative towards the healthy side.

In the case of a central vertigo, HIT can be negative.

The evaluation of the HIT should never be separated from the evaluation of the nystagmus and those of the other maneuvers suggested by the algorithm.

Videos of "Characteristics of nystagmus and HIT in a case of peripheral vestibulopathy and in a case of cerebellar stroke can also be found in Ref. [20]".

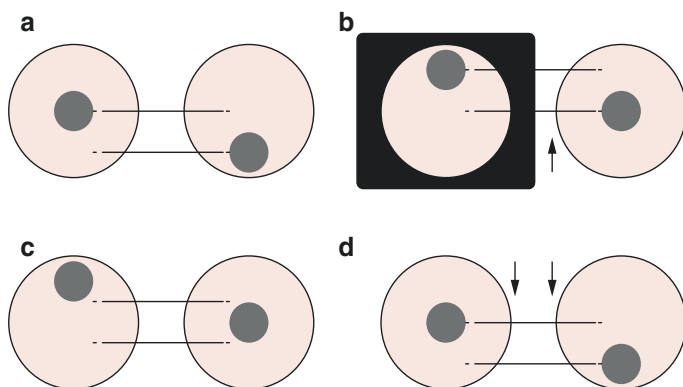
Cover Test (or Test of Skew)

Execution: The examiner alternately covers the patient's eyes; the appearance of a re-fixing saccade immediately after the uncovering of each eye, determined by the presence of a misalignment in the vertical plane, is an indicator of vertigo of central origin.

A sample of the Test of skew in a case of lateral medullary ischaemia can be found in Ref. [20].

Figure 8.2 illustrates an example of skew deviation during a cover test. In box A, there is a hypotropia of the left eye, that is, when binocular vision allows the fusional mechanisms, the left eye is lower than the right eye. If the right eye is covered, the left eye must move upwards to fixate the target and, considering that the two eyes move in a conjugated way, the right eye will also move upwards (box B). In the case of skew deviation (box B), the neuronal signal necessary to move the left eye of the desired amplitude will move the right eye of the same amplitude: the movement amplitude will be the same in the two eyes (arrows), and the distance between the two eyes (horizontal dashed lines) will not change. This will be confirmed when the right eye is uncovered: the degree of misalignment shown in box C is the same as that shown

Figure 8.2 Example of skew deviation during a cover test



in box A; moreover, if the target is fixated with the right eye, the downward movement of the two eyes will again have the same width (box D, arrows).

HINTS Evaluation

Some authors have proposed the unification of the three previous tests (nystagmus, HIT, and cover test) into a single test called HINTS [20].

HINTS is an eye movement test, performed at the bedside of a patient undergoing acute vestibular syndrome, to differentiate a central cause from an acute peripheral vestibulopathy. The acronym comes from the three tests in which the exam is divided: head impulse, nystagmus, test of skew.

Interpretation: HINTS evaluation is considered as suggestive for a peripheral lesion site (abnormal HIT + unidirectional horizontal nystagmus + absent skew deviation) or central (normal HIT, or multidirectional nystagmus, or skew deviation). The acronym INFARCT can help to store the signs of central HINTS (impulse normal, fast-phase alternating nystagmus, refixation on cover test).

The algorithm states that in the absence of nystagmus, positioning maneuvers must be carried out.

Positioning Maneuvers

Dix-Hallpike Manoeuvre

Execution: Before the manoeuvre, the patient should be informed that vertigo may occur. The patient should be seated on the couch and then turn his head 45° to the side to be evaluated; the open-eyed patient should stare at the examiner's eyes or at a farther target. The examiner holds the patient's head in his hands and quickly places the patient lying on the couch with the neck in hyperextension. In case of benign paroxysmal positional vertigo, the nystagmus appears within a few seconds (2–20 s latency) and

lasts for 20–40 s, when the head is rotated on the affected side. The test is negative if no nystagmus appears after 30 s and must therefore be repeated on the opposite side.

Interpretation: This maneuver has a positive predictive value of 83% and a negative predictive value of 52% for the diagnosis of benign paroxysmal positional vertigo (BPPV).

Appendix 1. Migraine with Brainstem Aura [21, 22]

Diagnostic Criteria

- A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
- B. Aura with both of the following:
 - 1. At least two of the following fully reversible brainstem symptoms:
 - ☐ Dysarthria [1]
 - ☐ Vertigo [2]
 - ☐ Tinnitus
 - ☐ Hypacusis [3]
 - ☐ Diplopia [4]
 - ☐ Ataxia not attributable to sensory deficit
 - ☐ Decreased level of consciousness (GCS ≤ 13) [5]
 - 2. No motor [6] or retinal symptoms.

Notes

- 1. Dysarthria should be distinguished from aphasia.
- 2. Vertigo does is not synonymous with and should be distinguished from dizziness.
- 3. This criterion is not fulfilled by sensations of ear fullness.
- 4. Diplopia is not synonymous with (nor does it excude) blurred vision.
- 5. The Glasgow Coma Scale (GCS) score may have been assessed during admission; alternatively, deficits clearly described by the patient allow GCS estimation.

6. When motor symptoms are present, code as 1.2.3 *Hemiplegic migraine*.

Comments

Originally the terms *basilar artery migraine* or *basilar migraine* were used, but, since involvement of the basilar artery is unlikely, the term *migraine with brainstem aura* is preferred.

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura*.

Many of the symptoms listed under criterion B1 may occur with anxiety and hyperventilation and are therefore subject to misinterpretation.

Appendix 2. Vestibular Migraine [23]

Diagnostic Criteria

- A. At least five episodes fulfilling criteria C and D
- B. A current or past history of 1.1 *Migraine without aura* or 1.2 *Migraine with aura* [1]
- C. Vestibular symptoms [2] of moderate or severe intensity [3], lasting between 5 min and 72 h [4]
- D. At least half of episodes are associated with at least one of the following three migrainous features [5]:
 - 1. Headache with at least two of the following four characteristics:
 - (a) Unilateral location
 - (b) Pulsating quality
 - (c) Moderate or severe intensity
 - (d) Aggravation by routine physical activity

2. Photophobia and phonophobia [6]
3. Visual aura [7]
- E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder [8].

Notes

1. Code also for the underlying migraine diagnosis.
2. Vestibular symptoms, as defined by the Bárány Society's Classification of Vestibular Symptoms and qualifying for a diagnosis of A1.6.6 *Vestibular migraine*, include:
 - (a) Spontaneous vertigo:
 - ☐ Internal vertigo (a false sensation of self-motion)
 - ☐ External vertigo (a false sensation that the visual surround is spinning or flowing)
 - (b) Positional vertigo, occurring after a change of head position
 - (c) Visually induced vertigo, triggered by a complex or large moving visual stimulus
 - (d) Head motion-induced vertigo, occurring during head motion
 - (e) Head motion-induced dizziness with nausea (dizziness is characterized by a sensation of disturbed spatial orientation; other forms of dizziness are currently not included in the classification of vestibular migraine).
3. Vestibular symptoms are rated *moderate* when they interfere with but do not prevent daily activities and *severe* when daily activities cannot be continued.
4. Duration of episodes is highly variable. About 30% of patients have episodes lasting minutes, 30% have attacks for hours, and another 30% have attacks over several days. The remaining 10% have attacks lasting seconds only, which tend to occur repeatedly during head motion, visual stimulation, or after changes of head position. In these patients, episode duration is defined as the total period during which short attacks recur. At the other end of the spectrum, there are patients who may take 4 weeks to recover fully from an episode. However, the core episode rarely exceeds 72 h.

5. One symptom is sufficient during a single episode. Different symptoms may occur during different episodes. Associated symptoms may occur before, during, or after the vestibular symptoms.
6. History and physical examinations do not suggest another vestibular disorder *or* such a disorder has been considered but ruled out by appropriate investigations *or* such a disorder is present as a comorbid condition but episodes can be clearly differentiated. Migraine attacks may be induced by vestibular stimulation. Therefore, the differential diagnosis should include other vestibular disorders complicated by superimposed migraine attacks.

Other Symptoms

Transient auditory symptoms, nausea, vomiting, prostration, and susceptibility to motion sickness may be associated with A1.6.6 *Vestibular migraine*. However, since they also occur with various other vestibular disorders, they are not included as diagnostic criteria.

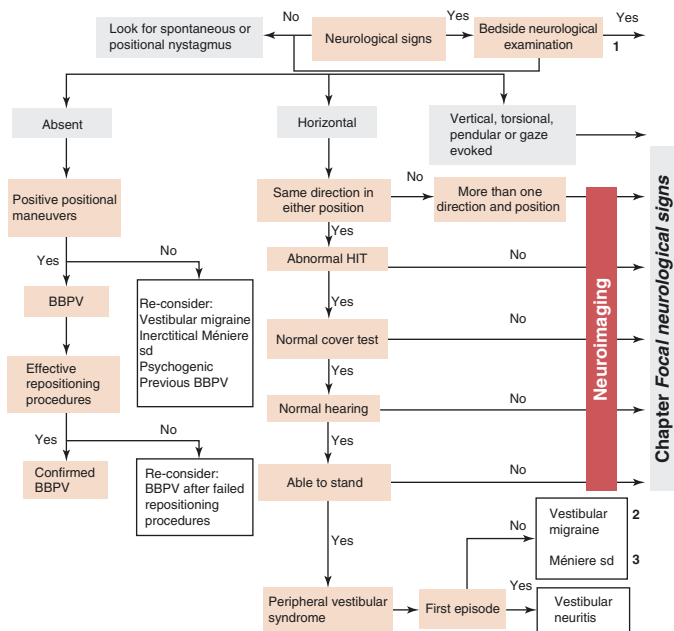
Relation to Migraine Aura and Migraine with Brainstem Aura

Both *migraine aura* and *migraine with brainstem aura* (formerly: *basilar-type migraine*) are terms defined by ICHD-3. Only a minority of patients with A1.6.6 *Vestibular migraine* experience their vertigo in the time frame of 5–60 min as defined for an aura symptom. Even fewer have their vertigo immediately before headache starts, as required for 1.2.1.1 *Typical aura with headache*. Therefore, episodes of A1.6.6 *Vestibular migraine* cannot be regarded as migraine auras.

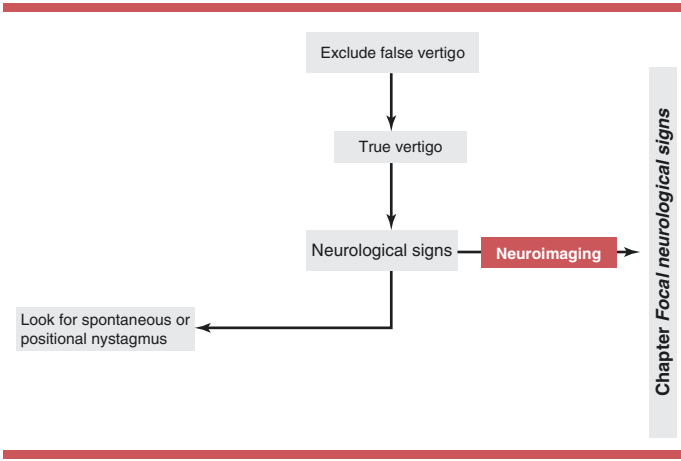
Although vertigo is reported by more than 60% of patients with 1.2.2 *Migraine with brainstem aura*, ICHD-3 requires at least two brainstem symptoms in addition to visual, sensory, or dysphasic aura symptoms for this diagnosis. Fewer than 10% of patients with

A1.6.6 *Vestibular migraine* fulfill these criteria. Therefore, A1.6.6 *Vestibular migraine* and 1.2.2 *Migraine with brainstem aura* are not synonymous, although individual patients may meet the diagnostic criteria for both disorders.

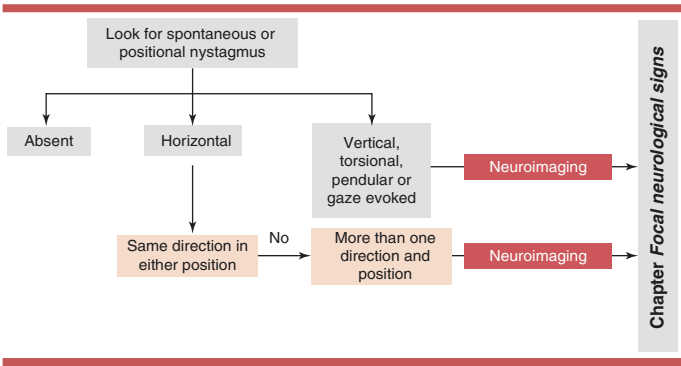
Appendix 3. Diagnostic Algorithm



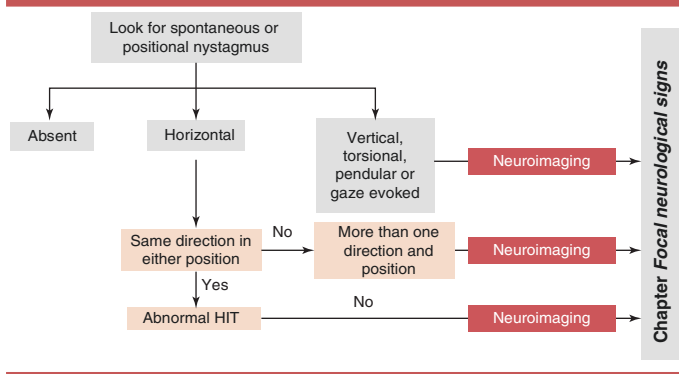
Diagnostic Algorithm A



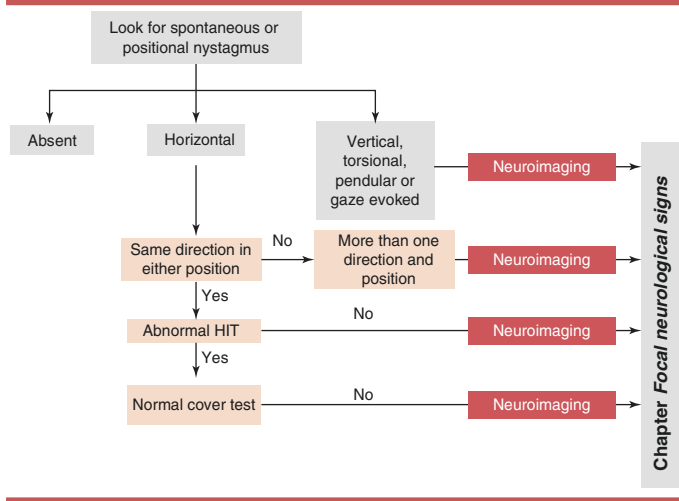
Diagnostic Algorithm B



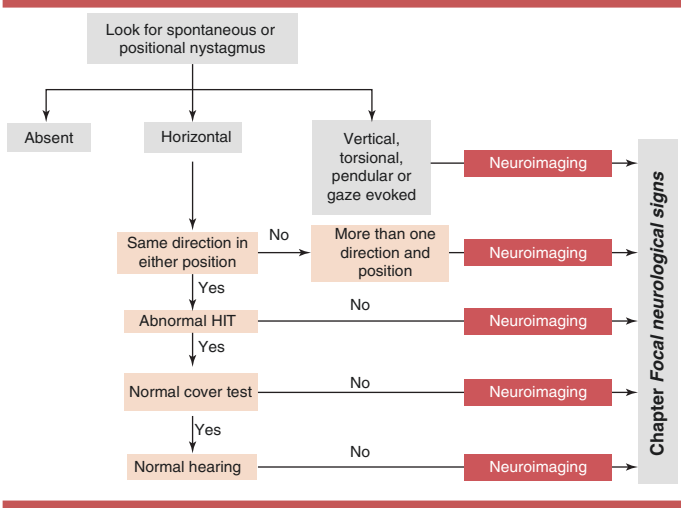
Diagnostic Algorithm C



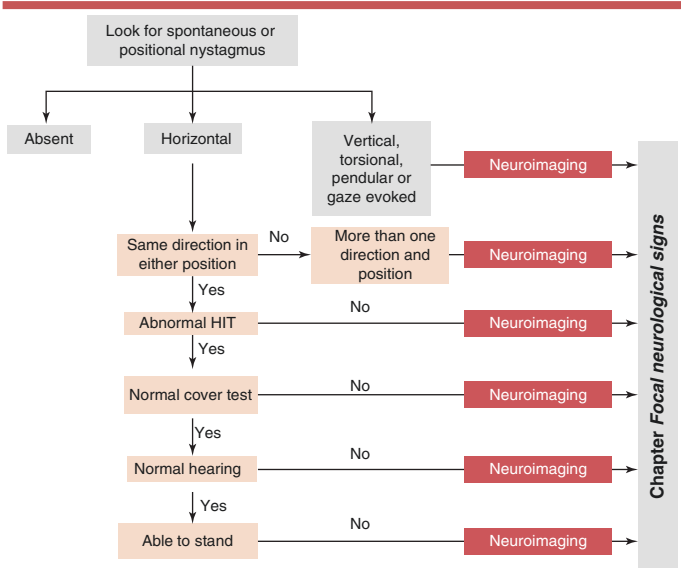
Diagnostic Algorithm D



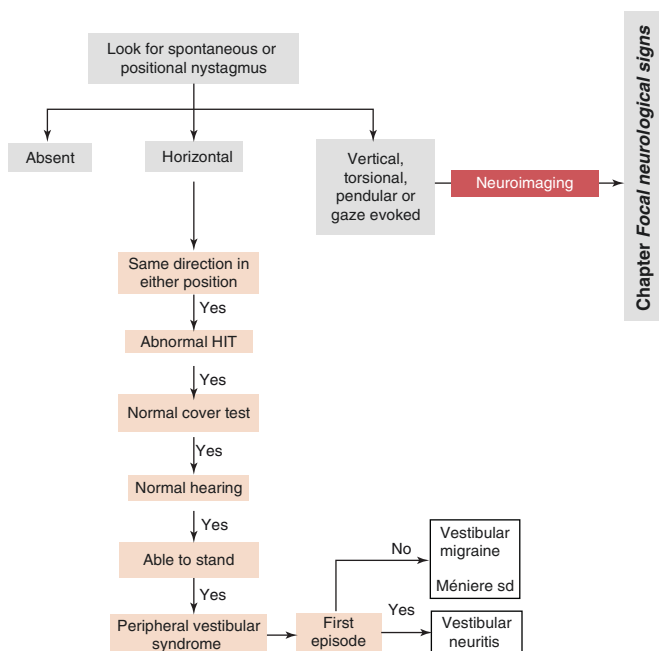
Diagnostic Algorithm E



Diagnostic Algorithm F



Diagnostic Algorithm G



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9. Diagnostic Algorithm for Patients Presenting with Acute Dizziness: The ATTEST Method

Jonathan A. Edlow

Introduction

Approximately 3–4% of all patients presenting to a general emergency department (ED) have a chief complaint of dizziness [1]. Because so many different conditions can cause this symptom, physicians need to use some organized data-driven algorithmic approach that will both minimize useless testing and also help make a specific diagnosis whenever possible [2–5]. In addition, front line physicians should always attempt to exclude dangerous diagnoses that might lead to poor patient outcomes if incorrectly managed. In the USA, several billions of dollars are spent annually on ED patients with dizziness [6].

Historically, the diagnostic approach to patients with dizziness was based on the “symptom quality” of the dizziness. That is to say, the work-up of the patient who endorses “vertigo” would be different

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than the work-up of a patient who endorses “lightheadedness” or “unsteady gait” [7]. This approach (which suggests that the first question to ask a dizzy patient is, “What do you mean, ‘dizzy?’”) has been taught for decades across all specialties, including neurology, ear-nose-and-throat (ENT), and internal and emergency medicine.

The methodological shortcomings of this landmark paper have been recently outlined. Research done in the last 10 years has shown that this “symptom quality” approach is intrinsically flawed [5, 8, 9]. Implicit in this “symptom quality” approach is that each word has diagnostic significance and also that patients will reliably and consistently report only 1 type of dizziness, neither of which is true.

In fact, basing the differential diagnosis and work-up simply on the word that the patient endorses is not helpful. Patients with benign paroxysmal positional vertigo (BPPV) will often complain of “dizziness” or “lightheadedness” and not “vertigo” [10, 11]. This is especially true in older patients. In addition, patients with cardiovascular causes of dizziness, who *should* complain of “lightheadedness,” endorse vertigo nearly 40% of the time [12]. In another study, ED patients with dizziness were asked a series of questions to determine their dizziness “type” and also some of the temporal aspects of the dizziness. When re-surveyed again within less than 10 min, using the same questions but in a different sequence, 50% of the patients changed their dizziness subtype [13]. In addition, patients frequently endorsed 2 or 3 dizziness types simultaneously. The responses to timing and triggers of the dizziness were much more consistent between the two surveys. Throughout this chapter, I will use the term “dizziness” to mean any of these dizziness types because there is no diagnostic utility separating them out [14].

This has led to a newer diagnostic approach based on “timing and triggers” of the dizziness [2, 3, 5, 8, 15–17]. There are several timing and triggers categories that are tightly associated with a specific differential diagnosis (Table 9.1). My diagnostic algorithm (Fig. 9.1) can be used to try to distinguish which dizzy patients in the ED have dizziness due to a general medical (toxic, metabolic, or infectious) problem versus a vestibular or central nervous system problem and to make a specific diagnosis in the latter groups.

Table 9.1 Timing and trigger-based “vestibular” syndromes^a in acute dizziness^b

Syndrome	Description	Common benign causes	Common serious causes	Important less common causes
AVS	Acute, continuous dizziness lasting days, accompanied by nausea, vomiting, (often) nystagmus, head motion intolerance, and gait unsteadiness	<ul style="list-style-type: none"> • Vestibular neuritis • Labyrinthitis 	<ul style="list-style-type: none"> • Posterior circulation ischemic stroke 	<ul style="list-style-type: none"> • Multiple sclerosis • Wernicke’s encephalopathy
s-EVS	Episodic dizziness that occurs spontaneously is not triggered ^c and usually lasts minutes to hours	<ul style="list-style-type: none"> • Vestibular migraine • Menière’s disease 	<ul style="list-style-type: none"> • Posterior circulation TIA 	<ul style="list-style-type: none"> • Panic attack • Arrhythmia • Transient low flow state • Pulmonary embolism • Aortic stenosis

Continued

Table 9.1 Continued

Syndrome	Description	Common benign causes	Common serious causes	Important less common causes
t-EVS	Episodic dizziness brought on by a specific, obligate trigger (typically a change in head position or standing up), and usually lasting less than 1 min	<ul style="list-style-type: none"> • BPPV 	<ul style="list-style-type: none"> • CPPV • Orthostatic hypotension due to serious medical illness 	<ul style="list-style-type: none"> • SCDS • Vertebral artery compression

AVS acute vestibular syndrome, *t-EVS* triggered episodic vestibular syndrome, *s-EVS* spontaneous episodic vestibular syndrome, *BPPV* benign paroxysmal positional vertigo, *CPPV* central paroxysmal positional vertigo, *TIA* transient ischemic attack, *SCDS* superior canal dehiscence syndrome

^aNote that the use of the word “vestibular” here connotes vestibular symptoms (dizziness or vertigo or imbalance or lightheadedness, etc.), rather than underlying vestibular diseases (e.g., benign paroxysmal positional vertigo, vestibular neuritis)

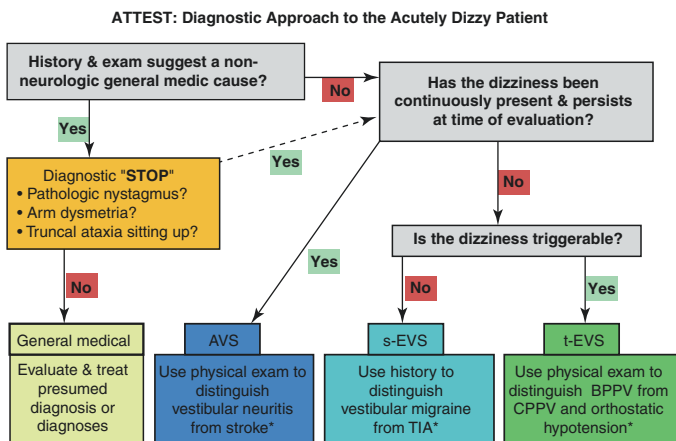
^bThis table lists the more common or important diseases causing these presenting syndromes and is not intended to be exhaustive

^cDizziness is “triggered” (not dizzy at baseline, dizziness develops with movement), as in positional vertigo due to BPPV. This must be distinguished from dizziness that is “exacerbated” (dizzy at baseline, worse with movement); such exacerbations are common in AVS, whether peripheral (neuritis) or central (stroke)

Misdiagnosis

Misdiagnosis of dizzy patient is common, in part due to this traditional diagnostic paradigm, even among neurologists. In a German study of 475 ED patient with dizziness all assessed by a neurologist, the diagnosis was changed at a subsequent visit by a second neurologist blinded to the initial diagnosis nearly half of the time [18]. One of the causes identified for misdiagnosis was seeing the

Figure 9.1 Diagnostic algorithm



* For each vestibular syndrome, only the most common benign and dangerous diagnoses are listed

patients early in their course, which of course is often the case for the first physician. There is also a “needle-in-the-haystack” problem. Only a very small minority of dizzy patients in an ED population have cerebrovascular diagnoses. In a study of nearly 1700 adult patients in the ED with dizziness, fewer than 1% of those who presented with isolated dizziness had a cerebrovascular cause [19]. Multiple studies have found that the proportion of ED patients with dizziness discharged with a benign “peripheral” diagnosis and who were subsequently hospitalized with a stroke diagnosis ranged from 0.14% to 0.5% [20–23]. So although the proportion misdiagnosed is small, it is a small proportion of a very large number of patients.

This chapter will not discuss in detail all of the literature on misdiagnosis of dizzy patients which has been recently reviewed [5, 8, 24, 25]. However one last comment is that the frequency of misdiagnosis depends on study methodology. Studies using a “look forward” approach (frequency of all dizzy patients in an ED population who later found to be misdiagnosed) [26–28] will find a much lower misdiagnosis rate than studies using a “look backwards” approach (e.g., frequency of misdiagnosis in all patients later

presenting with cerebellar strokes who had been seen in an ED at an earlier visit) [29]. Risk factors for stroke misdiagnosis include younger age of the patient, vertebral dissection as a cause, and a presentation of dizziness [30–32]. Other causes of misdiagnosis include knowledge gaps regarding the ocular motor exam and over-reliance on CT scanning [33–35].

Diagnostic Algorithm

The approach that I use is called the ATTEST method (Fig. 9.1) [2–5, 9].

- A: Associated symptoms
- TT: Timing and triggers
- ES: Exam signs
- T: Testing (additional testing, if needed)

The first step—associated symptoms—is simply acquiring some context and doing a review of systems that one would do with any other patient. One would never ask a patient with chest pain, “what you mean ‘chest pain’?” and then base the differential diagnosis and testing exclusively on the word that the patient uses. Although the descriptor of “sharp” or “tearing” chest pain suggests a diagnosis of aortic dissection, a patient with “tearing” chest pain intermittently over the prior week, which only occurs when they walk upstairs carrying a bag of groceries and resolves within minutes upon rest, suggests unstable angina and not aortic dissection.

A patient with dizziness who also has vomiting and diarrhea after eating undercooked food suggests gastroenteritis with dehydration. A febrile dyspneic patient with dizziness and a cough productive of green sputum suggests pneumonia or bronchitis. Dizziness with vaginal bleeding, abdominal pain, and a missed menstrual period suggests an ectopic pregnancy. Therefore, the first step of the evaluation of a dizzy patient is the same as it is with any other patient, taking a complete history and looking at the vital signs to look for patients that have some type of general medical condition causing the dizziness and not asking “what do you mean, ‘dizzy’?”

If the cause seems to be a general medical cause, then the presumed diagnosis should be further evaluated and treated. Before taking this step, it may be useful to perform a brief diagnostic STOP, to quickly (this should take less than 1 min) evaluate for worrisome nystagmus, cerebellar function, or truncal ataxia.

At this point in the algorithm, one poses questions to define a timing and triggers category. In patients with acute dizziness, there are three major categories, each of which will be further defined and discussed in the next section:

- *Acute vestibular syndrome (AVS)*: the acute onset, often abrupt of dizziness lasting many hours to days (or sometimes weeks) associated with gait instability, head motion intolerance, often nausea and vomiting and usually (but not always) nystagmus.
- *Spontaneous episodic vestibular syndrome (s-EVS)*: episodes of dizziness of variable duration (minutes to hours) that spontaneously start and stop and which are not triggered by anything.
- *Triggered episodic vestibular syndrome (t-EVS)*: brief episodes of dizziness usually lasting less than 1 min that are always provoked by some trigger, usually motion of the head, or standing up.

History

AVS

In patients with the AVS, dizziness begins rapidly or abruptly and is continuously present. By definition, it is present at the time that the physician evaluates the patient in the ED. These patients are intolerant to head motion. It is important to recognize that in a patient who is already dizzy to start with, worsening with head motion does not mean that the process is peripheral, a common misconception [36]. A distinction must be made between a patient who is completely asymptomatic at rest and who then develops dizziness with motion (triggered dizziness) and dizziness that is present but mild at rest which gets worse with head motion (exacerbated dizziness).

Strictly speaking, the presence of nystagmus is incorporated into the definition of the AVS. However, as many as 50% of patients

with a cerebellar infarction do not have nystagmus [37]. Because they present with acute dizziness, I do not include nystagmus as a necessary part of the AVS. This is an important distinction as it relates to how one interprets the head impulse test (HIT) discussed below. Nausea and vomiting are also common in the AVS.

Although there are many causes of the AVS, three conditions account for approximately 97% of cases [38]. Most common, accounting for roughly 75% of cases, is vestibular neuritis. The second most common and the most serious, posterior circulation stroke accounts for approximately 20%. Multiple sclerosis accounts for another 2–3% [38, 39]. A large number of other conditions account for the remaining 2% or 3% [38]. One important diagnosis to consider because it is so easily treatable is acute thiamine deficiency, Wernicke's encephalopathy, which can present with an AVS and is treatable with thiamine repletion [40].

s-EVS

In patients with the s-EVS, the dizziness occurs in discreet episodes between which the patient is asymptomatic. These patients are by definition asymptomatic when they are evaluated in the ED. If they are still symptomatic, one should apply the same approach (see section "Physical Examination") as for patients with an AVS. Because, again by definition, these patients are both asymptomatic and the dizziness is not triggerable at the bedside, the evaluation is entirely based on history [3, 8]. The most common cause of the s-EVS is vestibular migraine. The most serious but less common cause of the s-EVS is posterior circulation transient ischemic attack (TIA) [41]. Although posterior circulation TIA manifesting as isolated dizziness has traditionally been thought to be rare, newer data suggest that it precedes posterior circulation stroke in approximately 8% of cases [42]. Emphasizing the concept that the "type" of dizziness is diagnostically unimportant, in a study of 1265 consecutive patients presenting to an outpatient TIA/minor stroke clinic, nonfocal symptoms occurred in nearly 20% of patients [43]. Non-rotatory dizziness (the most common nonfocal symptoms) occurred in 174 (14%) of these patients and was more common in patients with posterior circulation ischemia. The

third most common diagnosis in this category is Ménière's disease, although in an unselected ED population, this is an uncommon cause.

t-EVS

In patients with a *t-EVS*, the most common cause is orthostatic hypotension in an ED population. These symptoms are usually triggered by standing up from the seated or lying down position. Orthostatic hypotension may be benign or serious depending on its cause. Another very common cause of *t-EVS* is BPPV. Dizziness that occurs while the patient is lying down, especially at nighttime, strongly suggests BPPV and would be very unusual with orthostatic hypotension [44]. Because the symptoms are triggerable, they can be reproduced at the bedside, and the physical examination is very useful in patients with the *t-EVS*.

One rare cause of episodic dizziness that is triggered by loud noises (the Tullio phenomenon) or Valsalva is the superior canal dehiscence syndrome (SCDS). This is caused by dehiscence of the thin layer of bone over the superior portion of the superior (anterior) semicircular canal so that intracranial pressure is rapidly transmitted to the vestibular apparatus [45]. Another rare cause is positional vertebral artery compression that can lead to posterior fossa ischemia when a vertebral artery is compressed with turning of the head (bow hunter's syndrome), often by a bony spur [46]. Triggered dizziness can also occur with compression of the brainstem by an abnormal vertebral artery [47].

Physical Examination

It should be clear from the prior section that physical examination can be extremely helpful in making a diagnosis in patients with an *AVS* or a *t-EVS* but is not useful in patients with an *s-EVS* [2, 5, 8, 24, 45]. In an "all-comers" group of patients with dizziness, such as those who present to an ED or a physician's office, approximately half of them will not have one of these vestibular syndrome's but rather have dizziness as part of their presentation

of a general medical (toxic, metabolic, or infectious) condition [1]. As described in the prior section, a standard history aimed at defining the context and associated symptoms that occur with the dizziness will usually identify these types of conditions. In the remainder of this section, we will focus exclusively on the various vestibular syndromes.

AVS

Not only is the physical examination useful in patients with an AVS, it is actually more useful than MRI scanning, at least in patients who present within the first 48 h [48–50]. In the hands of neuro-otologists, studies show that the so-called HINTS testing is nearly 100% sensitive in distinguishing peripheral causes of the AVS from central causes [48–50]. Studies done by stroke neurologists and by emergency physicians with specialized training and using Frenzel lenses also show that the HINTS testing can be done accurately [51–53]. However, it is not known if general neurologists, internal medicine, or emergency medicine physicians can perform and interpret these examinations in routine practice with the same accuracy. Because of this, I recommend that physicians also do a neurological exam targeted at the posterior circulation-fed structures, as well as gait testing (Table 9.2) [4, 5, 8, 16]. Adding these two elements to the testing should improve the safety when the evaluation is performed by physicians who are not subspecialists.

HINTS is an acronym for a group of bedside ocular motor tests—the head impulse, nystagmus, and test of skew deviation tests. Despite the order of the letters in the acronym, I test for nystagmus first for several reasons [4, 5, 8, 16]. Firstly, it is easily tolerated by the patient who does not need to move their head at all. Secondly if a patient with an AVS does not have nystagmus in the first several days of the illness, vestibular neuritis is an extremely unlikely cause, and, finally, because the HIT has not been validated in patients without nystagmus, it is unclear how one should interpret the results of the HIT in this group of patients.

Table 9.2 Sensitivity of various components of the physical examination for central mechanism in patients with the acute vestibular syndrome

Component of exam	Sensitivity for central cause ^a (%)	Comments
Nystagmus	50–60	See Table 9.3
Skew deviation	25	This finding is not very sensitive but specific for a central etiology, usually in the brainstem
Head impulse test ^b	85–90	Extremely important to <u>only</u> use this test in patients with the AVS with nystagmus. Other patients will have a “negative” test, which is “worrisome” for a stroke
Focused neurological exam	65	In addition to obvious neurological findings, it is important to look for subtle findings that can be easily missed
Gait and/or truncal ataxia	65	This is an essential test in patients with dizziness. Some patients without the first four findings may be unable to sit up or stand and walk unaided. Apart from obvious disposition issues, many of these patients will have a stroke

Abbreviations: AVS acute vestibular syndrome

^aApproximate numbers based on pooled data from multiple studies in some cases

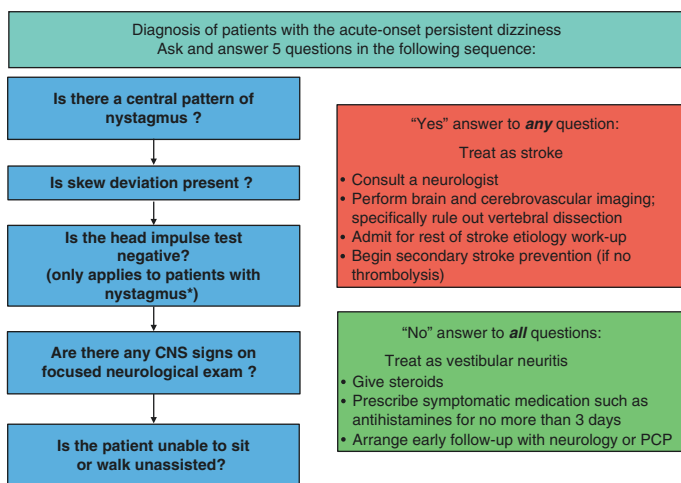
^bFor AVS patients with nystagmus, the combined sensitivity of the first three elements (HINTS) approaches 100%, when done by neuro-otologists

For all of these reasons, I ask five questions in this sequence (Table 9.2 and Fig. 9.2):

1. Is there a central pattern of nystagmus?
2. Is skew deviation present?
3. Is the HIT negative (no corrective saccade)?
4. Are there any central nervous system findings on focused posterior circulation exam?
5. Is the patient unable to sit or walk unassisted?

If the answer to any one of these five questions is “yes,” then the patient probably has a central cause of their AVS, most likely stroke, and should be admitted to the hospital for neurological consultation

Figure 9.2 Diagnostic algorithm for differentiating vestibular neuritis from stroke in patients with the acute vestibular syndrome. This sequence of testing is largely based on the HINTS (head impulse-nystagmus-test of skew) model, but the sequence is different (see text for reasons), and there are two additional components—targeted neurological exam that specifically directed towards the cerebellum and brainstem and testing for truncal and gait ataxia. I recommend these other components of the diagnostic algorithm because the HINTS testing has not been validated when used by emergency physicians under routine circumstances. In one study, adding gait testing to the HINTS exam plus hearing yielded 100% sensitivity for stroke. Furthermore, testing gait in any dizzy patient is important to ensure a safe disposition, even if the cause is peripheral. Abbreviations: *CNS* central nervous system, *PCP* primary care physician



* In patients **without** nystagmus, the head impulse test may give misleading results; the focused neurological exam and gait assessment become more important in this group (see text)

and further evaluation and treatment. If the answer is "no" to all five questions, the patient most likely has vestibular neuritis and can be discharged on prednisone with outpatient neurology or ENT follow-up.

Testing for nystagmus starts by observing what the patient's eyes do in the neutral or primary gaze—looking straight ahead. The examiner

looks to see whether the eyes are moving or not. By convention, nystagmus is named by the direction of the fast component from the patient's perspective. Therefore, horizontal nystagmus that is beating to the patient's left is called left-beating nystagmus. Vertical nystagmus whose fast component is beating upwards is termed upbeating nystagmus. After examining the patient in primary gaze, have the patient look to both sides and up and down. If the direction of the fast component of the nystagmus changes direction when the patient shifts their gaze to the left and right (following the examiner's finger), they have "gaze-evoked nystagmus." In patients with the AVS, gaze-evoked nystagmus, or nystagmus that is torsional, or vertical is always central (Table 9.3). It is important to note that some patients will have physiological end-gaze nystagmus, the changes direction depending on direction of gaze. The nystagmus is very low amplitude and usually extinguishes rapidly. This is a normal finding.

Table 9.3 Nystagmus and skew deviation interpretation in patients with the acute vestibular syndrome

Finding	Significance	Comments
No nystagmus	Normal finding	Essentially rules out vestibular neuritis but is consistent with a cerebellar stroke. Some patients with BPPV will endorse continuous dizziness and not have nystagmus at rest
Spontaneous horizontal nystagmus in primary gaze	Does not distinguish between central and peripheral causes	Seen more commonly with peripheral causes of AVS but is not diagnostic. In neuritis, may have a slight torsional component
Gaze evoked horizontal nystagmus that beats in only one direction	Does not distinguish between central and peripheral causes	Suggests a peripheral cause of AVS but is not diagnostic. In neuritis, may have a slight torsional component
Direction-changing gaze evoked horizontal nystagmus (see explanation below)	Central	Note: this is always central but can be a benign central cause (e.g., acute alcohol intoxication or anticonvulsant use). Some patients have physiologic end-gaze nystagmus that is a normal finding (see text)

Continued

Table 9.3 Continued

Finding	Significance	Comments
Pure vertical nystagmus	Central	In the ED, this should always be considered a central finding
Torsional nystagmus	Central	Note that torsional nystagmus is the expected finding in posterior canal BPPV, but these patients do not present with the AVS but rather a triggered episodic vestibular syndrome. There is often a slight torsional component in neuritis
Skew deviation (see below)	Normally absent; its presence means a central cause	Not very sensitive but very specific; if present, this should be considered to be a central cause of the AVS

(1) Nystagmus is nearly always present in vestibular neuritis but only seen in 50% of cerebellar stroke patients and variably in other brainstem strokes. Therefore, it is the quality of the nystagmus that is diagnostically important, not the mere presence or absence. Absence of nystagmus essentially excludes a diagnosis of acute vestibular neuritis or “labyrinthitis” if the patient is examined carefully in the first several days of the illness. (2) To test for nystagmus, ask the patient simply open their eyes and look directly forward to see if there is nystagmus in primary gaze. Then have them look to the right then the left. If the fast component of the nystagmus changes direction (i.e., is right beating on rightward gaze and left beating on leftward gaze), this is central finding. In vestibular neuritis, the nystagmus is primarily horizontal with a slight torsional component. (3) Test skew deviation by using the alternate cover test. With the patient’s eyes focused on a target (the examiner’s nose), the examiner alternately covers and then uncovers each eye, every 2–3 s. It is important to focus just on one eye (it does not matter which one) in order to see the small amplitude vertical corrections that occur when one eye is uncovered (one eye will go up and the other down, so either one will have a vertical correction, which is why either eye can be observed)

Abbreviations: AVS acute vestibular syndrome, ED emergency department, BPPV benign paroxysmal positional vertigo

Next one performs the alternate cover test to look for skew deviation (Table 9.3). Instructing the patient to stare directly at the examiner’s nose, the physician rapidly and alternately covers one eye then the other, going back and forth every second or so. Skew deviation is the presence of a small vertical correction, which is easier to see if the examiner focuses only on one eye or the other.

It does not matter which eye one focuses on because as one side goes up, the other will go down. Normally, there is no vertical correction. A horizontal correction is not skew deviation, only a vertical correction, which usually localizes to the brainstem.

Next one performs the HIT (Fig. 9.3—HIT). For this test too, the patient fixes their gaze on the examiner's nose. The patient's head should be "loose" and relaxed, and the active head movements done by the examiner should be very rapid but very small amplitude (~ 10 – 15°). Normally, the patient's eyes stay locked on target—the examiner's nose. The presence of a corrective saccade (eyes move with the head then snap back on target) usually indicates a peripheral vestibular localization except in two circumstances—a stroke involving the vestibular nerve root entry zone (usually in the anterior inferior cerebellar artery territory—AICA) or a labyrinthine infarct (i.e., a "stroke" of a peripheral structure but one fed by a branch of the AICA) [4].

The final two steps include performing a neurological examination that targets the structures fed by the posterior circulation—brainstem, cerebellum and occipital lobes, and then gait testing (Table 9.4). Findings of cranial neuropathy, abnormal finger-to-nose or heel-to-shin testing, or a visual field cut indicate a central cause. Last, one must test the gait in dizzy patients. The inability to stand or sit up without assistance is more likely to be of a central cause and in addition would indicate an unsafe discharge to home even if the cause is peripheral. In a study of 114 patients with the AVS, the inability to walk was far more common in stroke patients compared with vestibular neuritis patients [54]. In this study, all the patients with an AICA stroke who had a falsely reassuring HIT were unable to walk, emphasizing the importance of testing the gait.

s-EVS

History is used to try to distinguish between vestibular migraine, posterior circulation TIA, and Meniere's disease—the three most common causes of a *s-EVS*, at least in an ED population. Table 9.5 shows some of the distinguishing characteristics, with the caveat that there can be overlap and that these characteristics have not

Figure 9.3 Head impulse test. The head impulse test (HIT) is positive (abnormal) in nearly all patients with a peripheral cause of the acute vestibular syndrome (AVS) and negative (normal) in 85–90% of patients with a central cause of the AVS. It cannot therefore be used as a stand-alone test. It is only validated in patients with an AVS with nystagmus. The HIT tests the vestibulo-ocular reflex (VOR), which coordinates the eyes and stabilizes the image of a moving target. The afferent limb of the reflex loops from the peripheral vestibular labyrinth via the vestibular nerve to the vestibular nuclei in the brainstem, which in turn connects with the cranial nerve nuclei (3, 4, and 6) that move the eyes. The efferent limb for the horizontal HIT is the third and sixth cranial nerves that control horizontal eye movements. Because the reflex does NOT loop through the cerebellum, patients with cerebellar strokes will have a normal HIT. Occasional patients with strokes that affect the vestibular nucleus or the eighth nerve root entry zone in the brainstem will have a positive HIT. These strokes involve the anterior inferior cerebellar artery (AICA). The other less common explanation is that the stroke is of the labyrinth—a stroke involving the labyrinthine artery (a branch of the AICA). A key point is that if this test is applied in patients without the AVS with nystagmus, it can give misleading information

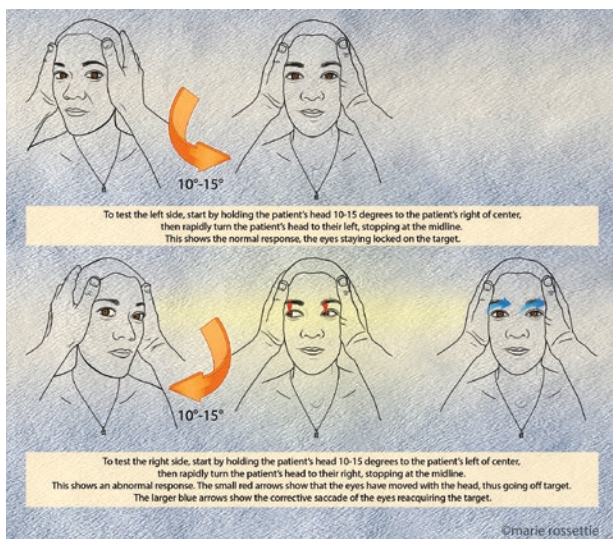


Table 9.4 Important components of the focused exam for posterior circulation stroke in patients presenting with the acute vestibular syndrome

Exam component	Significance	Comments
Hearing by finger rub in each ear	Can be central or peripheral	The classic teaching that dizziness plus decreased hearing is nearly always peripheral is wrong. Infarcts of the labyrinth or eighth nerve root entry one (AICA distribution) will also cause this combination of findings
Extraocular movements	If diplopia is present, this should be considered central	The nuclei of these three cranial nerves (3 and 4, midbrain, 4 and 6, upper pons) suggest a brainstem localization
Ptosis	Suggests a lateral medullary infarct	Part of Horner's syndrome
Anisocoria	Suggests a lateral medullary infarct	Seen best in a dark room to accentuate the difference in pupillary size. Part of Horner's syndrome
Facial weakness	Suggests a lesion in the internal auditory canal or brainstem	Standard seventh nerve testing
Decreased facial pain and temperature sensation	Suggests a lateral medullary infarct	Light touch is preserved, so one must test pain or temperature
Hoarseness (listening to the patient speak)	Suggests a lateral medullary infarct	Be careful about administering oral medications in this setting
Limb ataxia (finger-to-nose and heel-to-shin)	Cerebellar stroke	In the dizzy patient, these findings should be tested but may be absent in some patients with cerebellar strokes

Continued

Table 9.4 Continued

Exam component	Significance	Comments
Truncal ataxia	Cerebellar or brainstem stroke	Test the ability of the patient to maintain in the seated position unassisted in the stretcher without holding on to the guard rails for support
Gait ataxia	Cerebellar or brainstem stroke	Test the ability of the patient to stand and walk unassisted. Patients with neuritis may have some unsteadiness but usually can stand and walk, whereas many patients with stroke cannot

Abbreviations: *AICA* anterior inferior cerebellar artery

Table 9.5 Diagnostic criteria for vestibular migraine and clues to distinguish it from posterior circulation TIA in patients with the spontaneous episodic vestibular syndrome

- At least five episodes with vestibular symptoms^a of moderate^b or severe intensity lasting between 5 min and 72 h
- Present migraine or previous history of migraine with or without aura (according to the International Classification of Headache Disorders)
- One or more migraine features with at least 50% of the vestibular episodes
 - Headache with at least two of the following characteristics: unilateral location, pulsatile quality, moderate or severe pain, and aggravation by routine physical activity
 - Photophobia or phonophobia
 - Visual aura
- No other vestibular explanation

Patients with s-EVS due to vestibular migraine (compared to s-EVS patients with posterior circulation TIA) are more likely to be younger, have a history of migraine, have more vascular risk factors, have longer duration spells (greater than 1 h), and have more episodes over a longer period of time. Unfortunately, no one criterion is diagnostic

^aSpontaneous, positional or visually induced vertigo, head motion-induced dizziness with nausea

^bVertigo is “moderate” if interferes with but does not preclude daily activities and “severe” if it prohibits daily activity

been prospectively validated. It is important to note that patients with vestibular migraine may or may not have a headache, and if they do, the headache can precede, follow, or occur during the episode of dizziness. Although vestibular migraine represents a small proportion of patients with migraine, because migraine is so common in the general population, vestibular migraine is the most common cause of s-EVS [55]. A history of migraine, multiple previous episodes over a long period of time and younger age also favor this diagnosis [3].

Like most TIAs, posterior circulation TIA usually lasts less than an hour, has an abrupt onset and offset, and tends to occur in older patients with vascular risk factors. A long history of multiple spells would make TIA less likely [3]. One retrospective study of patients with episodic vertigo found that a smaller number of spells (<5 per week) and a presentation of isolated dizziness were both associated with a cerebrovascular cause of dizziness [56]. As in many TIA patients, even of the anterior circulation, brain imaging, even with MRI is often normal. One preliminary study suggested that MRI perfusion imaging might help to make identify patients with a cerebrovascular cause of episodic dizziness with negative DWI-MRI [57]. Clues to the diagnosis of Meniere's disease are aural fullness and tinnitus during an episode and decreased hearing over time [58, 59]. One study of 117 patients with episodic dizziness found that using patient-applied miniature video-oculography goggles at home was helpful in making the diagnosis of vestibular migraine, Meniere's disease, and BPPV [60]. Finally, a variety of general medical and psychiatric conditions can occasionally present with an episodic vestibular syndrome [61].

t-EVS

In patients with the t-EVS, physical examination is extremely useful in sorting out the major differential diagnosis of orthostatic hypotension and BPPV. In patients whose symptoms suggest orthostatic hypotension, measuring the vital signs with the patient lying

in bed and standing will make this diagnosis, recording the pulse, systolic, and diastolic blood pressure but also any orthostatic type symptoms that the patient has. Further diagnostic testing is directed at looking for a cause of the orthostatic hypotension.

In patients whose histories suggest BPPV, provocative maneuvers of the semicircular canals will make this diagnosis (Table 9.6). Usually the posterior semicircular canals are tested first because they are more gravity dependent and therefore much more common

Table 9.6 Physical examination maneuvers and findings that are used to diagnose and treat the typical forms of BPPV

Canal involved, mechanism (proportion of BPPV cases)	Provocative diagnostic maneuver/test	Expected type of nystagmus ^a	Therapeutic maneuver
pc-BPPV (80–85%)	Dix-Hallpike	Upbeating (from patient's perspective) and torsional ^b	Epley maneuver Alternative: Semont maneuver
hc-BPPV (15–20%) (sometimes called lateral canal)			
– Canalolithiasis (majority of horizontal canal cases)	Supine head roll	Geotropic (beats towards the floor) horizontal that is transient ^c Occurs on both sides, but is more intense on the <u>affected</u> side	Lempert barbeque roll maneuver Alternative: Gufoni maneuver
– Cupulolithiasis (minority of horizontal canal cases)	Supine head roll	Apogeotropic (beats towards the ceiling) horizontal, that is, persistent Occurs on both sides but is more intense on the <u>healthy</u> unaffected side	Gufoni maneuver

Table 9.6 Continued

Canal involved, mechanism (proportion of BPPV cases)	Provocative diagnostic maneuver/test	Expected type of nystagmus ^a	Therapeutic maneuver
sc-BPPV (~1–2%) (sometimes called anterior canal)	Dix-Hallpike	Downbeating vertical nystagmus ^d	Can use Epley, but this form of BPPV usually resolves spontaneously

Abbreviations: *BPPV* benign paroxysmal positional vertigo, *pc* posterior canal, *hc* horizontal canal, *sc* superior canal

^aAlthough the Dix-Hallpike test is fairly specific to *pc*-BPPV and the supine roll test is fairly specific to *hc*-BPPV, the maneuvers may sometimes stimulate the other canal. If so, the nystagmus direction will depend on the affected canal, not on the type of maneuver eliciting the nystagmus (e.g., if a Dix-Hallpike test is done on a patient with *hc*-BPPV, the nystagmus will be horizontal, not upbeat torsional). Also, the nystagmus may be considerably weaker and less obvious than if one was using the “correct” canal-specific maneuver

^bOn Dix-Hallpike testing, the nystagmus of *pc*-BPPV will have a prominent torsional component. The 12 o’clock pole of the eye will beat towards the down-facing (tested) ear. Upon arising from the down position, the nystagmus will reverse direction because the otoliths are now moving in the opposite direction

^cOn supine head roll testing, the nystagmus of *hc*-BPPV may beat towards the floor (geotropic—usually due to canalolithiasis) or towards the ceiling (apogeotropic—usually due to cupulolithiasis). When the other side is tested, the nystagmus will usually beat towards the opposite direction (e.g., if right-beating initially with right ear down, then it will usually be left-beating initially with left ear down). This is because the otoliths are now reversing their direction within the horizontal canal

^dDownbeating nystagmus can be seen with *sc*-BPPV. However, because *sc*-BPPV is very uncommon and because downbeating nystagmus is often the result of central structural lesions, it is safer for emergency physicians to consider this a worrisome finding prompting imaging and/or specialty consultation or referral

to be the offending canal. Usually this is done with the Dix-Hallpike maneuver, and if this is unilaterally positive, one treats with a canal re-positioning maneuver, usually the Epley or Semont maneuver. In patients with likely BPPV whose Dix-Hallpike test is negative, one should test the horizontal (lateral) canal using the supine head roll test and, if this is positive, treating the patient with a

Table 9.7 Characteristics of patients with t-EVS that suggest a central mimic (CPPV) rather than typical BPPV

-
1. Presence of symptoms or signs that are NOT seen in BPPV
 - (a) Headache
 - (b) Diplopia
 - (c) Abnormal cranial nerve or cerebellar function
 2. Atypical nystagmus characteristics or symptoms during positional tests
 - (a) Downbeating nystagmus^a
 - (b) Nystagmus that starts instantaneously, persists for longer than 90 s, or lacks a crescendo-decrescendo pattern of intensity
 - (c) Prominent nystagmus with mild or no associated dizziness or vertigo
 3. Poor response to therapeutic maneuvers
 - (a) Repetitive vomiting during positional maneuvers
 - (b) Unable to cure patient with canal-specific canalith repositioning maneuver^b
 - (c) Frequent recurrent symptoms
-

^aDownbeating nystagmus can be seen with anterior canal BPPV. However, because BPPV of this canal is rare and because downbeating nystagmus is most often the result of central structural lesions, it is safer for emergency physicians to consider this finding always worrisome prompting imaging and/or specialty consultation or referral

^bModified Epley maneuver or equivalent for posterior canal BPPV. Barbecue maneuver or equivalent for horizontal canal BPPV

Lempert barbecue roll. The superior (anterior) canal is very rarely involved and can be diagnosed and treated similar to the posterior canal.

If the history strongly suggests BPPV, but these maneuvers do not clarify the diagnosis, consider the very uncommon possibility of CPPV (Table 9.7) in which a structural lesion such as stroke or tumor abuts the fourth ventricle. In this situation, specialty consultation and brain imaging, which are not normally indicated or necessary in BPPV patients, should be performed.

Testing

Frequently, after history and physical examination, there is a clear confident diagnosis that can be treated, but, at times, the diagnosis remains unclear. In these cases, further testing must be

individualized depending on the specific context of that individual patient. Testing might be blood tests or a CT angiogram of the chest or a pregnancy test and pelvic ultrasound, depending on the diagnoses that are being considered. Due to its serious limitations in diagnosing posterior fossa pathology, especially acute cerebrovascular events, non-contrast brain CT should not be used by itself to determine a safe discharge disposition.

Using this algorithm, physicians can often make a confident and specific diagnosis, which will lead to more timely diagnosis and treatment, better resource utilization, and likely improved patient outcomes.

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10.

Focal Neurological Deficits

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Introduction

From What Point of View Are We Observing the Phenomenon

The chapter on acute focal neurological deficits is very broad. In fact, any insult to the central nervous system, be it vascular, infectious, inflammatory, neoplastic, mechanical/traumatic, affecting a more or less extensive part of the brain, can give rise to the deficit of function or functions performed by that specific brain area and in fact determine a focal deficit, in relation to the somatotopic organization of nervous structures. A sudden appearance, rather than a subacute progression, of the deficit is not necessarily decisive for differential diagnostic purposes, because, besides a stroke, which typically occurs suddenly, also a traumatic event, an encephalitis, a neoplasm, especially if metastatic, and a demyelinating disease can sometimes begin in an acute way. Certainly, some anamnestic data, such as the age of the patient (in very young patients we have always to think to the possibility of a demyelinating disease), the report of traumatic events involving the head, the presence, or not of fever or more or less recent infectious diseases (such as chronic otitis or an ongoing endocarditis), a past medical history of known primary neoplasm, especially if pulmonary, are useful to contextualize the deficit (Table 10.1).

However, it is not infrequent that the anamnestic information is poor, as in the case of an aphasic patient or with altered state of consciousness up to the state of coma, with the impossibility of acquiring more detailed information on the clinical history.

In this context, the epidemiological data may be useful, i.e. the frequency with which the various diseases that may give rise to a focal neurological deficit occur in the general population, which allows a probabilistic approach to differential diagnosis. With an average incidence on the national territory of about 2.5 cases per 1000 inhabitants per year, stroke is by far the most frequent neurological disease one may deal with in an emergency room and, in particular, the most frequent cause of focal neurological deficit [1].

Table 10.1 Possible causes of focal neurological deficit

Ischaemic stroke/transient ischaemic attack
Haemorrhagic stroke
Subarachnoid haemorrhage (with possible parenchymal involvement—meningo-cerebral haemorrhage—or cranial nerve involvement)
Subdural haematoma
Epidural haematoma
Migraine aura
Cerebral vein thrombosis
Structural intracranial lesions:
• Primary or metastatic neoplasms
• Aneurysm/arteriovenous malformation
Focal epileptic seizure/Todd's paralysis
Multiple sclerosis and other inflammatory CNS diseases (sarcoidosis, vasculitis, etc.)
Metabolic disorders
• Hypo-hyperglycaemia
• Hypo-hypercalcaemia
• Hyponatraemia
• Wernicke's encephalopathy
• Central pontine myelinolysis
Infectious diseases
• Brain abscess
• Herpetic encephalitis (involvement of temporal poles), <i>Listeria monocytogenes</i> infection (brainstem involvement) or other infectious agents
• Meningitis/meningoencephalitis
• Epidural-subdural empyemas
Myasthenia
Inflammatory or compressive spinal cord disorders
Pathology of the peripheral nervous system (Guillain-Barré syndrome, mononeuritis, and radiculopathies with different aetiologies)
Hyperventilation and panic attacks
Somatization disorders

We have therefore chosen to set up the diagnostic process of focal neurological deficit in the emergency setting, starting from the point of view of cerebrovascular diseases. This choice is also reinforced by the fact that, in addition to hospitalization in Stroke units, a therapeutic measure valid for both ischaemic and haemorrhagic strokes, for ischaemic stroke (and hopefully in the future also for haemorrhagic stroke), there are specific therapeutic possibilities to be applied within the first hours of onset of symptoms; It follows that stroke is in fact not only the most frequent neurological disease but also the one potentially most successfully treatable in emergency (Table 10.2).

Table 10.2 Neurological diagnoses ordered by frequency in patients admitted to an emergency department

Diagnosis	Final diagnosis (<i>n</i> = 1679) %
Stroke	567 (33.8)
Epileptic seizures	349 (20.8)
Headache	117 (7)
Loss of consciousness	94 (5.7)
Confusional state	95 (5.7)
Peripheral nervous system disorders	72 (4.3)
Postural instability/vertigo	21 (1.3)
Cognitive disorders	77 (4.6)
Balance disorders	37 (2.2)
Multiple sclerosis	43 (2.6)
Coma	5 (0.3)
Infectious diseases	24 (1.4)
Psychiatric disorders	43 (2.6)
Subdural haematoma	22 (1.1)
Brain tumour	36 (2.1)
Non-neurological disorders	77 (4.6)
Miscellaneous	0

Modified by Moulin et al. [1]

Pathway Organization According to the Level of Complexity of the Hospital

The hospital scenario on the national territory is very heterogeneous, with rather different complexities of specialized approaches and available instrumental equipment. For this reason, for the management of certain emergencies, including stroke, many regions have planned a network of more complex secondary level structures, called hub centres, to which primary level peripheral structures of different complexity, called spoke centres or simple peripheral nodes, must be functionally connected.

The different possibilities of managing patients with focal neurological deficit according to the type of hospital will be described case by case in the text.

■ **Hospital facilities with high structural complexity**

In addition to Stroke units and advanced radiological diagnostic services, they have complex structures and skills such as interventional neuroradiology, neurosurgery, and vascular surgery, available 24 h a day.

■ **Hospital facilities with intermediate structural complexity**

Usually they do not have more complex structures and competences as interventional neuroradiology, neurosurgery, and vascular surgery, even if, given the highly varied Italian hospital reality, some of these may be equipped in whole or in part with structures and competences typical of hub centres, but with the difference that they are not available h24.

■ **Hospital facilities with minimal structural complexity**

Small- or medium-sized territorial hospitals, in which patients with neurological emergencies may be admitted, even in the absence of the relevant skills and specialized personnel. These hospitals must necessarily be equipped with operational connections with the centres of higher level, which allow the rapid transportation of patients who may need it, where necessary with the intervention of the pre-hospital emergency system (118). The connection may also include the use of telemedicine systems. In general, these hospitals have at least one h12 CT scan, which is available at night only with on call shifts.

Patients, who do not need to be transported to higher-level hospitals for specific skills, must be admitted, in the hospitals that received them, to the wards provided by the local organization, in which however they should receive the most appropriate care as indicated by the ISO-SPREAD guidelines [2]. According to the Action Plan of the European Stroke Organisation, the objective is to achieve $\geq 90\%$ of stroke patients admitted to a Stroke unit by 2030 [3].

Clinical Pictures

Focal Neurological Deficits

A focal neurological deficit is defined as the set of neurological signs and symptoms due to injury or dysfunction of a specific area of the central or peripheral nervous system (Tables 10.3, 10.4, 10.5, and 10.6).

Table 10.3 Injury sites and possible associated clinical pictures

Possible location of the lesion	Signs/symptoms
Hemispheric	Deficit in cortical function: aphasia, acalculia, visual-spatial deficit, agnosia, apraxia, hemianopia, or, more rarely, monocular or otherwise referred to as monocular deficit Motor and/or sensory deficit of a hemisoma, even isolated, i.e. without signs/symptoms of cortical dysfunction, either total (facio-brachio-crural) or partial (brachio-crural hemiparesis, monoparesis: in the latter case, differential diagnosis with peripheral disorders)
Subtentorial	Stupor or coma (acute onset) Tetraplegia (<i>locked-in</i> syndrome) Paralysis of one or more cranial nerves on one side and sensory and/or motor deficits on the other side (alternating syndrome) Bilateral or unilateral sensory and/or motor deficits Conjugated eye movement disorder Cerebellar dysfunction without or with ipsilateral long pathways deficit
Medullary	Motor and/or sensory deficit associated with one or more of the following characteristics: motor or sensory metamer level, mixed signs of upper motor neuron' and 'lower motor neuron', sensory dissociation, early impairment of sphincteric, and sexual functions
Nerves and nerve roots	Motor and/or sensory deficit limited to the distribution of a single peripheral nerve or nerve root, associated or not with painful symptoms NB: A total isolated paralysis (upper and lower part) of the facial muscles is a neurological deficit mainly due to suffering of the peripheral facial nerve

Patient with Altered State of Consciousness: Stupor/Coma

For the detailed treatment of the diagnostic-therapeutic pathway of the patient in a coma state, refer to the specific chapter. Here, we remind that, once the non-neurological causes of stupor/coma are excluded, with an accurate history (where possible) and with the mentioned laboratory tests, it is necessary to perform:

Table 10.4 Concomitant symptoms that may guide the aetiological diagnosis of focal neurological deficit

Concomitant symptoms	Possible aetiopathogenetic clue
Fever	<p>Meningoencephalitis (especially if confusion is present)</p> <p>In case of stroke:</p> <ul style="list-style-type: none"> • Assess endocarditis with septic embolus • Assess infectious process with destabilization of carotid plaque • Possible hyperthermia from stress reaction
Headache	<p>Migraine attack: a unilateral headache of moderate-to-severe intensity that accompanies or follows the onset of focal neurological symptoms; however, the aura may not be accompanied or followed by headache</p> <p>Subdural or epidural haemorrhage</p> <p>Expansive lesions</p> <p>In case of stroke:</p> <ul style="list-style-type: none"> • Latero-cervical or retro-orbital pain, especially in subjects with an history of traction or violent movements of the neck, in possible association with Horner's syndrome: suggestive for dissection of extra- or intracranial internal carotid artery (ICA) • Frontal pain due to stroke in the anterior cerebral artery (ACA) or ICA territory • Orbito-temporal pain due to stroke in the territory of the middle cerebral artery (MCA) (in 10–40% of cases without dissection) • Cervical-nuchal pain: if ipsilateral it can indicate steno-occlusion, even from dissection, of a vertebral artery (VA); if bilateral it can indicate steno-occlusion of the basilar artery (BA) (in 20–70% of cases without dissection) <p>Other cerebrovascular events:</p> <ul style="list-style-type: none"> • Accompanied by focal and/or generalized seizures at the beginning, suggestive for: <ul style="list-style-type: none"> – Cerebral venous thrombosis – Posterior reversible encephalopathy syndrome (PRES) – Reversible cerebral vasoconstriction syndrome (RCVS) – With sudden onset, described as the worst headache in life, other than the usual, or new onset, arising after exertion, which may be accompanied by loss of consciousness and/or associated with signs of meningeal irritation and/or focal neurological signs (hemiparesis and/or paralysis of the III or VI cranial nerve): clinical suspicion of subarachnoid haemorrhage (SAH)

Continued

Table 10.4 Continued

Concomitant symptoms	Possible aetiopathogenetic clue
Focal and/or generalized seizures at onset	In case of cortical lesions: <ul style="list-style-type: none"> • Differential diagnosis with cerebral venous thrombosis • Differential diagnosis with secondary epilepsy of other causes or with post-critical deficit
Confusion, psychomotor agitation, memory deficit	See Chap. 3

Table 10.5 Anamnestic data that may guide the aetiological diagnosis of focal neurological deficit

Onset of symptoms	Sudden appearance without premonitory signs (cerebrovascular event) Progression of symptoms in a few seconds (seizure) Progressive onset in minutes/hours (migraine aura) Progressive subacute onset lasting hours/days (inflammatory disease, encephalitis) Slow development of symptoms in weeks/months (space occupying lesion)
Duration of symptoms	Seconds/minutes (seizure) Minutes/hours (TIA, duration of symptoms less than 24 h, usually 1–2 h at most; migraine aura)
Nature of symptoms (<i>in descending order of probable aetiology</i>)	Negative symptoms and signs: loss of vision, motor deficit, cutaneous hypo-anaesthesia, aphasia (cerebrovascular event, migraine aura, space occupying lesions, inflammatory disease, seizure) Positive symptoms and signs: clonic spasms, choreic movements, ballistic movements, paresthesias/dysaesthesias, visual, auditory, olfactory, and gustatory disperceptive phenomena (seizures, migraine aura, space occupying lesions, cerebrovascular event)

Table 10.5 Continued

Additional signs and symptoms	<p>Onset in conjunction with physical effort, often accompanied by violent cervical-nuchal headache, suggestive for SAH</p> <p>Monolateral transient (amaurosis fugax) or persistent loss of vision in elderly subjects, possibly in association with pain in the temporal region, suggestive for temporal arteritis or athero-thromboembolic carotid disease</p> <p>Meningeal signs and symptoms, suggestive of meningitis/encephalitis</p> <p>Loss of consciousness, suggestive for SAH, intraparenchymal haemorrhage, brainstem cerebrovascular event, or large hemispheric stroke</p>
Age (<i>in descending order of probability</i>)	<p>Young person (migraine aura, aneurysm/arteriovenous malformation [AVM], ischaemic stroke, multiple sclerosis)</p> <p>Elderly person (stroke, neoplasm, metabolic disorders)</p>
Past medical history	<p>Concomitant autoimmune diseases (multiple sclerosis, vasculitis)</p> <p>Cardiovascular risk factors (ischaemic or haemorrhagic stroke)</p> <p>Known psychiatric conditions (panic attack, conversion disorder)</p>
Drugs	<p>Oral anticoagulant therapy (intraparenchymal-subarachnoid-subdural haemorrhage)</p> <p>Oral contraceptives (stroke, sinus thrombosis)</p> <p>Drug/alcohol abuse (ischaemic or haemorrhagic stroke, Wernicke's encephalopathy)</p>

Table 10.6 Differential diagnosis: stroke mimics

Posterior reversible encephalopathy syndrome (PRES)	<p>It is found in cases of eclampsia gravidarum, severe hypertensive conditions with/without renal failure, therapy with monoclonal antibodies, immunosuppressive therapies in transplanted patients</p> <p>Clinical picture: most frequently visual field disturbance up to blindness; possible slight focal sensory-motor neurological deficit. Generally, headache has been present for several days and very frequent partial seizures with possible secondary generalization (see Chap. 4), so that it enters into differential diagnosis especially with thrombosis of the venous sinuses</p> <p>Instrumental investigations: MRI FLAIR highlights slight signal hyperintensity in the white matter more often at the level of the occipital lobes (hence the name of the syndrome), but also possible at the basal nuclei and anterior areas or diffuse, which usually disappears in a few days following normalization of blood pressure</p>
Reversible cerebral vasoconstriction syndrome (RCVS)	<p>Reversible cerebral vasoconstriction syndrome is characterized by the presence of plurisegmental vasoconstriction of the intracranial arteries with acute-subacute onset, which tends to spontaneous regression</p> <p>Clinical picture: severe acute onset headache, usually of the ‘thunderclap’ type, sometimes associated with cerebral infarctions, intracranial haemorrhages, or cerebral oedema that can lead to the appearance of focal neurological deficits and/or epileptic seizures</p> <p>RCVS may be part of the PRES spectrum and may share its aetiological causes</p> <p>More frequently is related to the use of drugs with sympathetic activity. Instrumental investigation angiographic study of intracranial vessels by CT-angiography, MR-angiography, digital angiography (representing the gold standard), or transcranial Doppler</p> <p>Clinical course: generally benign with regression of the vasospasm in a variable period, usually 3 months, and without complications, with the aid of only symptomatic therapeutic measures. In selected cases, the elimination of a possible triggering factor and empirical treatment with calcium channel blockers can be considered</p>

Metabolic disorders	Hypoglycaemia: in a patient with focal motor deficit, always carry out an evaluation of capillary glycaemia; in case of hypoglycaemia, proceed as indicated in Chap. 2. Hyponatraemia: always think about this possibility, especially in elderly patients with a past medical history of heart, kidney, or liver failure, use of diuretics, carbamazepine, antidepressants (especially SSRI), especially if in association with each other or with ACE inhibitors or angiotensin receptor blockers
Seizure at onset and/or post-critical deficit	Especially in case of a negative or unclear past medical history of seizures See Chap. 4
Multiple sclerosis and other CNS demyelinating diseases	
Migraine aura	See Chap. 5
Sporadic hemiplegic migraine	See Chap. 5
Spondylogenic tetraparesis	See Chap. 11
ynversion/functional disorder	To be taken into account in particular in young patients, mainly but not exclusively females. Sometimes diagnostic suspicion induced by incongruity of symptoms or the presence of specific signs of functional disorder (e.g. Hoover's sign) Instrumental investigations: negative MRI images, including diffusion and perfusion sequences, in the presence of a clinically detectable focal deficit may be useful for diagnosis

- Brain CT and angio-CT, which can highlight (in about 20% of cases):
 - Hemispheric haemorrhage or SAH
 - Brainstem or cerebellar haemorrhage
 - Brainstem infarction, bi-thalamic infarction
 - Cerebral venous thrombosis

For the management of these clinical pictures, please refer to the respective paragraphs.

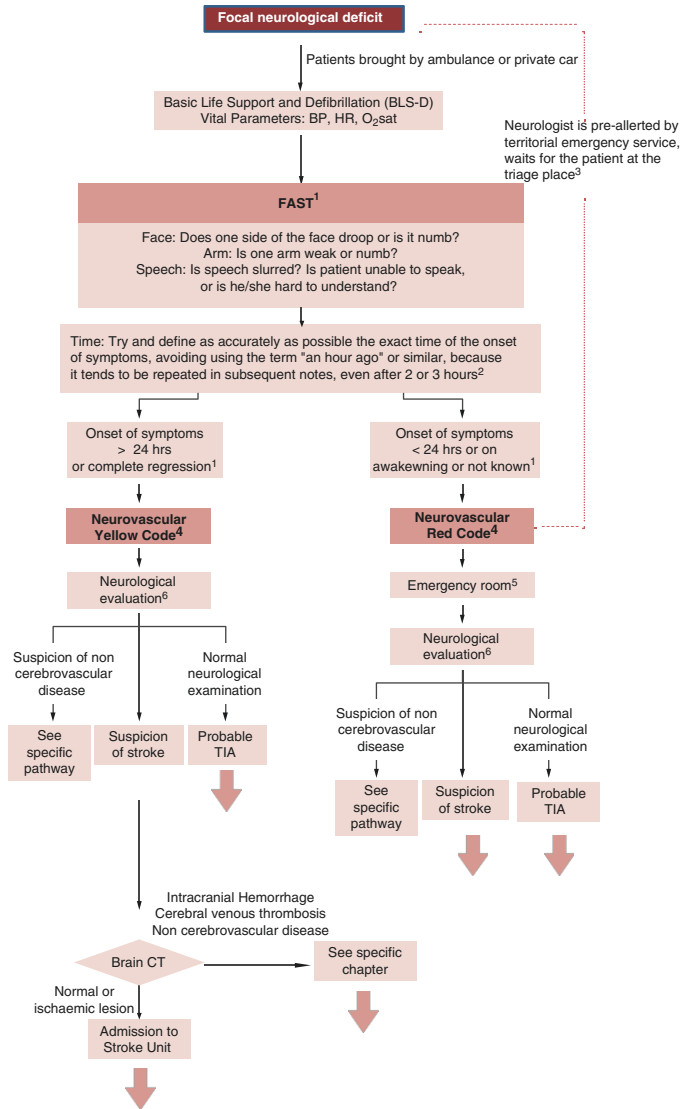
In the case of less complex facilities, consider transferring those patients who need intensive care management to higher-level centres.

Diagnostic Pathway of Ischaemic Stroke and Revascularization Treatments

The steps of the hospital phase (Fig. 10.1) are analysed below:

1. In the evaluation of an acute onset focal neurological deficit, triage staff may use the FAST scale (or, alternatively, the Cincinnati Prehospital Stroke Scale, CPSS). The FAST scale easily and quickly explores the most common focal neurological symptoms at onset of an acute cerebrovascular event and underlines the importance of determining the time of onset. The negativity of the symptoms on the scale does NOT exclude an acute cerebrovascular event (including transient ischaemic attack) and should NOT delay the patient's access to a medical assessment. It can be useful for the stratification of the patient's severity and for communication with medical staff and/or the pre-alerted neurologist at the emergency department.
2. It is important to define as accurately as possible the exact time of the onset of symptoms, avoiding using the term 'an hour ago' or similar, because it tends to be repeated in subsequent notes. In case of onset of symptoms upon awakening or in the absence of witnesses who can report the time in the aphasic patient, it must be specified both the reported or presumed time of awakening and the time when the patient was last seen/heard in well-being.
3. According to specific territorial organizations, the vascular neurologist may be alerted about the arrival of a patient with focal neurological deficit by the staff of the emergency system. In this case, the neurologist performs a preliminary clinical and anamnestic evaluation, in order to speed up the time of access to neuroimaging and then to any revascularization treatment.
4. The attribution of a severity colour code in the case of focal neurological deficit must take into account the urgency of

Figure 10.1 Stroke pathway



access to revascularization treatment and not only the criticality in terms of life hazard. In particular, a specific stroke code or neurovascular code must be established, distinguished in red or yellow grade in relation to the possibility of a reperfusion treatment.

5. Patient management in the emergency room:

- ☐ Resuscitation manoeuvres (if necessary), Advanced Cardiovascular Life Support, ACLS
- ☐ Monitoring of vital parameters (BP, HR, sat O₂, body temperature), body weight measurement with scale stretcher where available
- ☐ Venous line insertion (two in case of intravenous thrombolysis)
- ☐ 12 lead ECG
- ☐ Blood gas analysis
- ☐ Blood tests: blood count, electrolytes, BUN, creatinine, glycaemia, CPK, INR, and PTT
- ☐ Pregnancy test for women of childbearing age
- ☐ Extemporaneous bladder catheterization, after use of bladder scan if available
- ☐ Evaluation of pre-stroke disability: modified Rankin Scale (mRS—see below)
- ☐ Past medical history of risk factors: arterial hypertension, diabetes, smoking, dyslipidaemia, previous episodes of TIA/stroke, MI, arrhythmias, traumas, surgery, bleeding, and ongoing drug treatments

6. Neurological evaluation:

- ☐ Calculate the NIHSS score (Table 10.7)
- ☐ Calculate the GCS score (see Chap. 2)
- ☐ Physiological history: reported body weight (if body weight measured with scale stretcher is not available), pregnancy status
- ☐ Pathological history: disability prior to acute event (mRS, Table 10.8), arterial hypertension, diabetes mellitus, smoking, alcohol, drugs, dyslipidaemia, previous episodes of TIA/stroke, myocardial infarction or other ischaemic heart disease, arrhythmias (in particular history of palpitations or documented atrial fibrillation), traumas, surgery, previous haemorrhagic episodes, previous or current neoplasms,

Table 10.7 National Institute of Health Stroke Scale (NIHSS) score determination

Function to be examined—instructions	Scores
<p>1a. Level of consciousness: vigilance The examiner must choose a response even if a full assessment is difficult due to the presence of endotracheal tubes, language barrier, orotracheal trauma/ bandages. The score '3' is given only if the patient does not make any movement (other than reflexive posturing) in response to noxious stimulation</p>	<p>0. Alert, keenly responsive 1. Not alert, but arousable by minor stimulation to obey, answer, or respond 2. Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) 3. Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, are flexic</p>
<p>1b. Level of consciousness: orientation The patient should be asked first in which month we are and then his/her age. The answers must be correct: there is no partial credit for being close. If the patient is aphasic or stuporous (1a = '2') the score is '2'. If the patient cannot speak because of endotracheal intubation, orotracheal trauma, severe dysarthria, language barriers, or other problem not secondary to aphasia, the score is '1' It is important that only the initial answer be graded and that the examiner not 'help' the patient with verbal or non-verbal cues</p>	<p>0. Answers both questions correctly 1. Answers one question correctly 2. Answer neither question correctly</p>

Continued

Table 10.7 Continued

Function to be examined—instructions	Scores
<p>1c. Level of consciousness: understanding and executing simple orders The patient should be asked to open and close the eyes and then to grip and release the non-parietic hand. If the hands cannot be used, the order must be replaced with another simple command. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to the verbal command, the examiner can mimic the task and still give a score. Patients with trauma, amputation, or other physical impediments, should be given suitable simple commands. Only the first attempt is scored</p>	<p>0. Performs both tasks correctly 1. Performs one task correctly 2. Perform neither task correctly</p>
<p>2. Best gaze Only horizontal, voluntary, or reflexive (oculocephalic) eye movements are scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score is '1'. In case of isolated peripheral nerve palsy (III, IV, or VI cranial nerve), the score is '1'. Gaze is also evaluable in aphasic patients. In case of eye trauma, bandages, pre-existing blindness, or other disorders visual acuity or fields, the reflexive motility will be evaluated, and the score will be given at the discretion of the examiner. Establishing eye contact with the patient and then moving about the patient from side to side sometimes help to reveal the presence of partial paralysis of the gaze</p>	<p>0. Normal 1. Partial gaze palsy: gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present 2. Forced deviation of gaze, or total gaze paresis not overcome by the oculocephalic manoeuvre</p>

<p>3. Visual field</p> <p>The visual field (upper and lower quadrants) is evaluated by confrontation or by finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. In the presence of unilateral blindness or enucleation, the visual field of the healthy eye is scored. The score '1' should only be given in the case of clear-cut asymmetry, including quadrantanopia. In the presence of bilateral blindness, whatever its origin, the score is '3'. The test should be concluded with double simultaneous stimulation. If there is extinction, the score is '1', and the result is used to respond to item 11 (inattention)</p>	<p>0. Normal. Absence of field deficits</p> <p>1. Partial hemianopia (quadrantanopia)</p> <p>2. Complete hemianopia</p> <p>3. Bilateral hemianopia (includes bilateral blindness of any cause)</p>
<p>4. Facial paralysis</p> <p>The patient should be asked to show teeth, raise eyebrows, and close eyes. Requests can be mimed. In case of aphasia or poor collaboration, the symmetry of grimace in response to painful stimuli should be scored. If the patient has facial trauma/bandages, orotracheal tube, tape, or other physical barriers, obscuring the face, these should be removed to the extent possible</p>	<p>0. Normal. Symmetrical facial movements</p> <p>1. Minor paralysis. Flattened nasolabial fold, asymmetry on smiling</p> <p>2. Partial paralysis. Total or near-total paralysis of lower face</p> <p>3. Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)</p>

Continued

Table 10.7 Continued

Function to be examined—instructions	Scores
<p>5a. Motor activity of the left upper limb The upper limb should be positioned by the examiner with the palms downwards, at 90° if the patient is sitting or at 45° if the patient is supine. Drift is scored if the arm falls before 10 s. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimuli. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice</p>	<p>0. No drift, limb holds 90° (or 40°) for full 10" 1. Drift; limb holds 90° (or 45°) but drifts down before full 10 s; does not hit bed or other support 2. Some effort against gravity; limb cannot get to or maintain (if cued) 90° (or 45°), drifts down to bed, but has some effort against gravity 3. No efforts against gravity; limb falls 4. No movement UN = Amputation or joint fusion, explain: _____ As above</p>
<p>5b. Motor activity of the right upper limb As above</p> <p>6a. Motor activity of the left lower limb The lower limb should be examined by lifting it at an angle of 30° on a supine patient. The patient must hold the position for 5 s. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimuli. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice</p>	<p>0. No drift; leg holds 30° position for full 5 s 1. Drift; leg falls by the end of the 5-s period but does not hit bed 2. Some effort against gravity; leg falls to bed by 5 s but has some effort against gravity 3. No effort against gravity; leg falls to bed immediately 4. No movement UN = Amputation or joint fusion, explain: _____</p>

<p>6b. Motor activity of the right lower limb As above</p>	<p>As above</p>
<p>7. Limb ataxia This test is intended to detect a posterior circulation disturbance. Test with eyes open; in case of visual field deficit, make sure that the test is done in intact visual field. The index-nose and heel-knee test are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is considered absent in patient who cannot understand or is plegic. The NV score will be assigned only in case of amputation or ankylosis of the limb, providing written explanation</p> <p>8. Sensory Sensation or grimace to pinprick when tested or withdrawal from noxious stimulus in the obtunded or aphasic patient Only sensory loss attributed to stroke is scored as abnormal, and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, 'severe or total sensory loss', should only be given when a severe or total loss of sensation can be clearly demonstrated Stuporous and aphasic patients will, therefore, probably score 1 or 0 The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in coma (item 1a = 3) are automatically given a 2 on this item</p>	<p>0. Absent 1. Present either on upper or lower limb 2. Present on both upper and lower limbs NV. Amputation or joint fusion (explain)</p> <p>0. Normal: no sensory loss 1. Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched 2. Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg</p>

Continued

Table 10.7 Continued

Function to be examined—instructions	Scores
<p>9. Best language A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items of the attached naming list and to read from the attached list of sentences. Verbal comprehension is also assessed on the basis of the answers obtained in previous tests, including the general neurological examination. If a visual impairment interferes with the tests, the patient should be asked to identify the objects in his hand, repeat, and pronounce speech. The intubated patient should be asked to write a sentence. The patient in coma (question 1a = 3) is automatically assigned the score '3'. In case of stupor or limited collaboration, the examiner will choose the score remembering that '3' should be assigned only if the subject is mute and does not execute any order</p>	<p>0. Normal 1. Mild-to-moderate aphasia. In spontaneous speech, fluency or understanding is somewhat reduced, but ideas are expressed without significant limitations. Conversation on the attached material may be difficult or impossible, but the patient's answers allow the figure or objects named to be identified 2. Severe aphasia. The expression is fragmentary, and the listener is forced to ask questions and try to extrapolate the content from the answers. The amount of information exchanged is modest, and communication is only possible thanks to the effort of the listener. The patient's answers do not allow to identify the figure or the named objects 3. Mute, global aphasia. Fluency and understanding totally ineffective</p>

<p>10. Dysarthria</p> <p>Even if the patients is not considered to be dysarthric, speech should still be assessed by asking the patients to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of spontaneous language articulation can be evaluated. NV should only be assigned to a patients who is intubated or has other physical barriers to produce speech. However, a written explanation of why this score was provided must be given</p>	<p>0. Absent</p> <p>1. Mild-to-moderate dysarthria. The patient slurs at least some words, but the speech is understandable</p> <p>2. Severe dysarthria</p> <p>Patient's speech is so slurred as to be unintelligible in the absence of or out of proportion of any dysphasia, or the patient is mute/anarthric</p> <p>NV. Intubated or other physical barrier (explain)</p>
<p>11. Extinction and inattention</p> <p>Inattention can be identified by previous tests. In case of severe visual impairment that does not allow simultaneous double visual stimulation, and the skin stimuli are normal, the score is normal. If the patient is aphasic but shows normal attention to both sides, the score is normal. Visual-spatial neglect or anosognosia should be considered as evidence of inattention</p>	<p>0. Absent</p> <p>1. Visual, tactile, auditory, spatial, or personal inattention, or extinction to bilateral simultaneous stimulation in one of the sensory modalities</p> <p>2. Profound hemi-inattention or extinction to more than one modality. The patients does not recognize his/her own hand or orients only one side of the space</p>

Continued

Table 10.8 Modified Rankin Scale (mRS)

0. No symptoms	
1. Non-disabling symptomatology The patient is able to perform all the usual activities and tasks despite the presence of symptoms	Areas of physical/cognitive symptoms Difficulties in verbal expression, reading, or writing Difficulty in movements, sensations, vision, or swallowing Low mood The patient is able to carry out his/her previous work, social, or hobby activities Normal activities are those that are carried out at least monthly
2. Slight disability The patient is no longer able to carry out all the previous activities, but is autonomous in walking and in the activities of daily life	Inability to perform some of the usual activities before a stroke (e.g. driving a vehicle, working, reading) Able to take care of themselves without daily assistance (e.g. dressing, moving around the house, eating, personal hygiene, preparing simple meals, shopping, or short trips) Supervision is not required The patient can be left alone at home for periods of more than a week
3. Moderate disability Patient needs help in daily life activities but walks without assistance	Patient can move with the aid of a stick, crutch or 'walker' He/she is able to dress, take care of personal hygiene, and feed him/herself. He/she needs help with more complex tasks (e.g. shopping, cooking, or cleaning) Requires to be attended more frequently than once a week He/she needs supervision in the management of bureaucracy and personal finances
4. Moderately severe disability The patient is not able to walk without help or to take care of his/her essential needs	He/she is not able to move without the assistance of a third person He/she needs help with everyday activities (e.g. dressing, eating, or personal hygiene) He/she needs to be assisted on a daily basis The patient can be left alone only for short periods during the day
5. Severe disability Patient who is bedridden, incontinent, and/or needs constant care	Need for constant assistance during the day and possibly at night
6. Death	

ongoing therapies (in particular anticoagulant/antiplatelet drugs), and history of psychiatric disorder.

- Check the results of the 12-lead ECG (particularly for atrial fibrillation, signs of myocardial ischaemia).
- Check the results of blood tests (in particular for thrombocytopenia, dystonia, hypo-hyperglycaemia, troponin increase, alteration of the coagulative profile, pregnancy status in women of childbearing age).
- Verify that at least two venous lines have been inserted (useful when administering contrast medium for angio-CT and perfusional CT, or other drugs during rt-PA infusion). Routine bladder catheterization should be avoided. In case of thrombolysis, the need for occasional bladder emptying should be considered.

NOTE: The procedures described in steps 5 and 6 should be completed within a maximum of 10 min. In some centres the patient does not stop at the ED, but is taken directly to radiology for CT, where the neurologist also goes. Blood samples are taken in the ambulance, as is the ECG, while the BGA is not routinely determined.

Knowledge of INR is not essential before starting intravenous thrombolysis.

Revascularization treatments (Fig. 10.2)

1. Brain CT

The plain brain CT can detect:

- Negative CT scan or presence of early signs and/or evidence of ischaemic brain injury
- Intraparenchymal haemorrhage
- Subarachnoid haemorrhage
- Subdural haematoma
- Occupying space lesion
- Signs of suspected thrombosis of the venous sinuses
- Signs of suspected inflammatory disease
- Signs of suspected infectious diseases

In the case of ischaemic stroke, the brain scan may be negative, may reveal the ischaemic lesion as an area of hypodensity, or

Figure 10.2 Algorithm for revascularization treatments

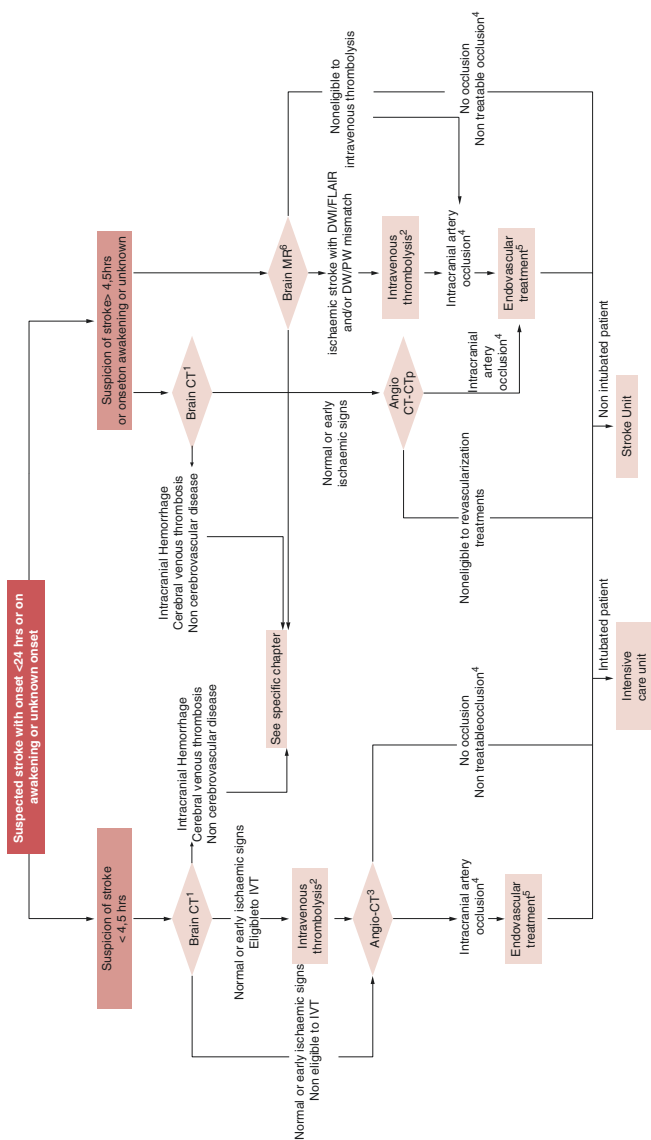
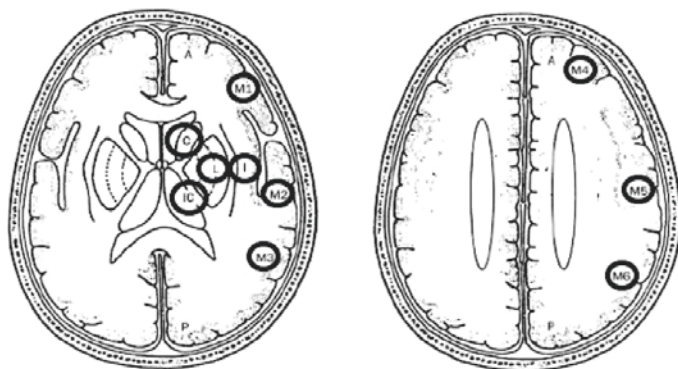


Figure 10.3 Calculation of the ASPECTS score



Legend:

C = caudate nucleus

IC = internal capsule

L = Lenticular nucleus

I = insula cortex

M1-M6 = cortical sulci

Total absence of early signs = 10

For each early sign subtract 1

Score > 7 = early signs not extended
(<1/3 MCA territory)

Score ≤ 7 = extended early signs (> 1/3
MCA territory) with high risk of:

- death/invalidity at 3 months;
- symptomatic intracerebral hemorrhage

may show the presence of early signs (sign of hyperdense MCA; middle cerebral artery dot sign; focal effacement of the cortical sulci with disappearance of the gradient between white and grey matter and/or focal compression of the ventricles; early hypodensity of the cerebral parenchyma).

The therapeutic diagnostic pathway continues with the calculation of the ASPECT (Alberta Stroke Programme Early CT) score (Fig. 10.3) [4].

Where available, the use of softwares for the automated calculation of the ASPECT score can facilitate the recognition of early signs of cerebral ischaemia and standardize the attribution of the score.

In the case of a probable posterior circulation stroke, brain CT may show initial areas of hypodensity of brainstem, cerebellum

and/or occipital regions of the brain, and/or the presence of a hyperdensity of the basilar artery (BA).

2. See '[Patient Eligibility for Intravenous Thrombolytic Treatment](#)'.
3. Depending on the facilities of each individual centre, the patient may be submitted to neck and intracranial vessel angio-CT immediately following cerebral CT showing the absence of intracranial bleeding or sent to a higher-level centre for advanced imaging. In this case, the patient should be transported to the reference centre as soon as possible; if systemic thrombolytic treatment is started, the infusion of the drug should NOT be interrupted, and the patient should be transported by ambulance with a doctor on board.

In any case, the execution of angio-CT should not delay the initiation of thrombolytic treatment if indicated.

Note: Where angio-CT is not routinely performed, a TCD/TCCD can be performed to limit requests of patient referral to a higher-level centre.

4. The term 'intracranial artery occlusion' refers to the occlusion of large cerebral vessels:

- Intracranial internal carotid artery (ICA)
- M1 or M2 part of the middle cerebral artery (MCA)
- A1 part of the anterior cerebral artery (ACA)
- Basilar artery (BA)
- Dominant vertebral artery (VA)
- P1 part of the posterior cerebral artery (PCA)

'No occlusion or non-treatable occlusion' means:

- No occlusion of intracranial arteries.
 - Occlusion of arterial branches other than those indicated above and not candidate to endovascular treatment.
 - The absence of eligibility criteria at perfusion CT or multi-modal brain MRI in patients with onset of symptoms >6 h (see '[Eligibility of the patient to endovascular treatment](#)') also falls within the definition of 'non-treatable occlusion'.
5. See '[Eligibility of the patient to endovascular treatment](#)'.
 6. In patients with suspected stroke more than 4.5 h after onset of symptoms or onset on awakening or unknown, based on specific protocols of each individual centre, it is possible to perform a specific neuroimaging examination as brain MRI or CT perfusion to identify patients treatable with IVT and/or EVT

according to the criteria specified in the sections 'Eligibility of the Patient to Intravenous Thrombolytic Treatment' and 'Eligibility of the Patient to Endovascular Treatment'.

Patient Eligibility to Intravenous Thrombolytic Treatment

Intravenous thrombolysis (IVT) should be performed in the Stroke unit or under the guidance of the vascular neurologist, according to protocols shared with other professionals involved, and in the absence of clinical contraindications, as soon as possible.

The following are the inclusion criteria and the absolute and relative exclusion criteria (Table 10.9) according to the ISO-SPREAD guidelines, to which reference should be made for a detailed description of the individual recommendations [2]. Below there is a dosage scheme of r-tPA in relation to weight (Table 10.10) and an example of a card for the monitoring of reperfusion treatments (Table 10.11).

Acute Complications of Intravenous Thrombolysis

In case of clinical deterioration during IVT, discontinue the infusion of the drug, and obtain urgent brain CT.

In the case of brain CT not showing intracerebral haemorrhage, thrombolytic infusion can be resumed, always within the time window for treatment.

In case of symptomatic intracerebral haemorrhage after r-tPA treatment (during infusion or within 24 h thereafter):

- Do not resume thrombolytic infusion.
- Ask for a neurosurgical evaluation.
- Give supportive therapy (strict control of blood pressure, glycaemia, body temperature).
- Consider the administration of alfa-aminocaproic acid or tranexamic acid (2 f iv in 10' every 8 h for 24 h, not to be administered if fibrinogen <100 mg/dl), factor VII, or PCC

Table 10.9 Intravenous thrombolysis: inclusion and exclusion criteria

Inclusion criteria	Yes	No
Patients of both sexes aged ≥ 16 years	<input type="checkbox"/>	<input type="checkbox"/>
Ischaemic stroke responsible for a measurable deficit of language, motor, cognitive, gaze, vision, and/or neglect	<input type="checkbox"/>	<input type="checkbox"/>
Stroke onset within 4.5 h of start of rt-PA administration	<input type="checkbox"/>	<input type="checkbox"/>
Stroke on awakening with mismatch between MR DW and MR FLAIR	<input type="checkbox"/>	<input type="checkbox"/>
Stroke onset between 4.5 and 9 h in the presence of savable ischaemic penumbra brain tissue (defined by DW/PW MRI or perfusion CT scan) ^a	<input type="checkbox"/>	<input type="checkbox"/>
Symptoms present for at least 30 min. Symptoms should be distinguished from those of an episode of generalized ischaemia (i.e. syncope), an epileptic seizure or a migraine attack	<input type="checkbox"/>	<input type="checkbox"/>
Patients (or a family member) should have received information about the treatment and possibly should have given consent to the use of their data and to follow-up procedures ^b	<input type="checkbox"/>	<input type="checkbox"/>
Absolute exclusion criteria	Yes	No
Stroke onset >4.5 h in the absence of any savable ischaemic penumbra brain tissue (defined by DW/PW MRI or perfusion CT)	<input type="checkbox"/>	<input type="checkbox"/>
Wake-up stroke in the absence of mismatch between MRI DW and MRI FLAIR	<input type="checkbox"/>	<input type="checkbox"/>
Intracranial haemorrhage on brain CT	<input type="checkbox"/>	<input type="checkbox"/>
Clinical suspicion of SAH, even if CT scan is normal	<input type="checkbox"/>	<input type="checkbox"/>
Intravenous heparin administration in the previous 48 h and aPTT exceeding normal upper laboratory limit	<input type="checkbox"/>	<input type="checkbox"/>
Current treatment with vitK antagonists and INR >1.7	<input type="checkbox"/>	<input type="checkbox"/>
Recent intake of non-reversible direct anticoagulant medication	<input type="checkbox"/>	<input type="checkbox"/>
Platelet count $<100.000/\text{mm}^3$	<input type="checkbox"/>	<input type="checkbox"/>
Known haemorrhagic diathesis	<input type="checkbox"/>	<input type="checkbox"/>
Ongoing or recent serious bleeding	<input type="checkbox"/>	<input type="checkbox"/>
Suspected intracranial haemorrhage	<input type="checkbox"/>	<input type="checkbox"/>
Bacterial endocarditis, pericarditis	<input type="checkbox"/>	<input type="checkbox"/>
Acute pancreatitis	<input type="checkbox"/>	<input type="checkbox"/>
Neoplasm with increased risk of bleeding	<input type="checkbox"/>	<input type="checkbox"/>
Severe liver disease, including liver failure, cirrhosis, portal hypertension (oesophageal varices), active hepatitis	<input type="checkbox"/>	<input type="checkbox"/>
Haemorrhagic retinopathy, e.g. vision disorders in diabetics	<input type="checkbox"/>	<input type="checkbox"/>
High risk of bleeding due to comorbidity	<input type="checkbox"/>	<input type="checkbox"/>
Recent (<10 days) traumatic external heart massage, childbirth, noncompressible blood vessel puncture (e.g. subclavian or jugular vein)	<input type="checkbox"/>	<input type="checkbox"/>
Ulcerative gastrointestinal disease (<3 months)	<input type="checkbox"/>	<input type="checkbox"/>

Table 10.9 Continued

Relative exclusion criteria ^c	Yes	No
Slight deficit or rapid improvement of symptoms (30 min)	<input type="checkbox"/>	<input type="checkbox"/>
Hour of onset unknown or stroke present upon awakening	<input type="checkbox"/>	<input type="checkbox"/>
Convulsive seizures at stroke onset	<input type="checkbox"/>	<input type="checkbox"/>
Patient with past medical history of stroke and concomitant diabetes	<input type="checkbox"/>	<input type="checkbox"/>
Blood glucose <50 or >400 mg/dl	<input type="checkbox"/>	<input type="checkbox"/>
Previous stroke in the last 3 months	<input type="checkbox"/>	<input type="checkbox"/>
Severe uncontrolled arterial hypertension	<input type="checkbox"/>	<input type="checkbox"/>
Severe stroke clinically (e.g. NIHSS >25) and/or on the basis of appropriate neuroimaging techniques	<input type="checkbox"/>	<input type="checkbox"/>
Oral anticoagulant therapy with vitK antagonists drug and INR ≤1.7	<input type="checkbox"/>	<input type="checkbox"/>
Recent intake of reversible direct anticoagulant medication	<input type="checkbox"/>	<input type="checkbox"/>
Anticoagulant therapy with low-molecular-weight heparins	<input type="checkbox"/>	<input type="checkbox"/>
Past medical history of CNS diseases: neoplasm, brain, or spinal surgery, aneurysm	<input type="checkbox"/>	<input type="checkbox"/>
Arterial aneurysm, arteriovenous malformation	<input type="checkbox"/>	<input type="checkbox"/>
Past medical of intracranial haemorrhage (parenchymal or subarachnoid)	<input type="checkbox"/>	<input type="checkbox"/>
Pregnancy	<input type="checkbox"/>	<input type="checkbox"/>
Major surgery or severe trauma (<3 months)	<input type="checkbox"/>	<input type="checkbox"/>

^aMost of the supporting studies used Rapid[®] software, but there are numerous and different systems for ischaemic core and perfusion calculation, not necessarily of equal accuracy and significance

^bFamily members have no legal power to decide on the execution of the therapeutic procedure (unless legal protection is already in place); they must be informed, and they may be asked if in the past the patient has expressed specific opinions about emergency-urgency treatments, but the final decision is still up to the doctor

^cExclusion criteria reported in the summary of characteristics of Actilyse[®] which are however not supported by scientific evidence reported in the literature [5]. Before and during treatment, monitor vital parameters (blood pressure, heart rate, body temperature, blood sugar), and evaluate neurological status by calculating the NIHSS score (see below)

Administer antipyretic therapy in case of fever ≥37.5 °C

Administer r-tPA 0.9 mg/kg (max 90 mg), 10% bolus in 1 min, the remainder infusion in 60 min

NB. The maximum dose of r-tPA is 90 mg, corresponding to a weight of 100 kg. For patients weighing ≥100 kg, the dose to be administered is always 90 mg

Table 10.10 Dosage scheme of r-tPA in relation to weight

Body weight (kg)	Total dose (mg = ml)	Bolus (mg = ml)	Infusion in 1 h by pump (ml/h)
55	49.5	4.9	44.6
56	50.4	5.0	45.4
57	51.3	5.1	46.2
58	52.2	5.2	47.0
59	53.1	5.3	47.8
60	54.0	5.4	48.6
61	54.9	5.5	49.4
62	55.8	5.6	50.2
63	56.7	5.7	51.0
64	57.6	5.8	51.8
65	58.5	5.9	52.7
66	59.4	5.9	53.5
67	60.3	6.0	54.3
68	61.2	6.1	55.1
69	62.1	6.2	55.9
70	63.0	6.3	56.7
71	63.9	6.4	57.5
72	64.8	6.5	58.3
73	65.7	6.6	59.1
74	66.6	6.7	59.9
75	67.5	6.8	60.8
76	68.4	6.8	61.6
77	69.3	6.9	62.4
78	70.2	7.0	63.2
79	71.1	7.1	64.0
80	72.0	7.2	64.8
81	72.9	7.3	65.6
82	73.8	7.4	66.4
83	74.7	7.5	67.2
84	75.6	7.6	68.0
85	76.5	7.7	68.9
86	77.4	7.7	69.7
87	78.3	7.8	70.5
88	79.2	7.9	71.3
89	80.1	8.0	72.1

Table 10.10 Continued

Body weight (kg)	Total dose (mg = ml)	Bolus (mg = ml)	Infusion in 1 h by pump (ml/h)
90	81.0	8.1	72.9
91	81.9	8.2	73.7
92	82.8	8.3	74.5
93	83.7	8.4	75.3
94	84.6	8.5	76.1
95	85.5	8.6	77.0
96	86.4	8.6	77.8
97	87.3	8.7	78.6
98	88.2	8.8	79.4
99	89.1	8.9	80.2
≥100	90.0	9.0	81

(increased thrombotic risk for administration of factor VII; likely increased thrombotic risk for tranexamic acid).

In case of oral angioedema:

- Maintain airway patency (intubation may not be necessary if oedema is limited to the anterior region of the tongue and/or lips); avoid nasotracheal intubation and cricotiroidectomy if possible because of the haemorrhagic risk associated with alteplase).
- Stop thrombolytic infusion.
- Not administer ACE inhibitor drugs.
- Administer steroids, antihistamines, and gastric protectors. If angioedema persists or increases, administer adrenaline or ica-tibant acetate (selective bradykinin B2 receptor antagonist; 30 mg sc in the abdominal region, repeatable after 6 h up to 60 mg/24 h).

Eligibility of the Patient to Endovascular Treatment

The following are the inclusion criteria according to the ISO-SPREAD/AINR guidelines on mechanical thrombectomy in acute ischaemic stroke, to which reference is made for a more detailed description of the recommendations (Table 10.12) [2].

Table 10.11 Example of a form for monitoring reperfusion treatments

Monitoring form of reperfusion treatments					
Patient	Last name	Date of birth		Name	
	Weight (kg)				
Time	Hour	ΔT^a	NIHSS	BP (mmHg)	Notes
Onset of symptoms					
Initial assessment					HGT: mg/dl
T_0 (Bolus)					
15'					
30'					
45'					
1 h					
1 h 15'					
1 h 30'					
1 h 45'					
2 h					
2 h 30'					
3 h					
3 h 30'					
4 h					
4 h 30'					
5 h					
5 h 30'					
6 h					
6 h 30'					
7 h					
8 h					
9 h					
10 h					
11 h					
12 h					
13 h					
14 h					
15 h					

Table 10.11 Continued

Monitoring form of reperfusion treatments					
16 h					
17 h					
18 h					
19 h					
20 h					
21 h					
22 h					
23 h					
24 h					

^a ΔT time from onset of symptoms

Table 10.12 Inclusion criteria for endovascular treatment within 6 h

Inclusion criteria	Yes	No
Age ≥ 18 years	<input type="checkbox"/>	<input type="checkbox"/>
Occlusion of the terminal tract of the internal carotid artery (ICA) and/or M1/M2 segment of the middle cerebral artery (MCA M1/M2)	<input type="checkbox"/>	<input type="checkbox"/>
NIHSS score ≥ 6	<input type="checkbox"/>	<input type="checkbox"/>
ASPECT score ≥ 6 on plain brain CT or ischaemic core volume ≤ 70 ml on perfusional CT	<input type="checkbox"/>	<input type="checkbox"/>
mRS pre-stroke 0–1	<input type="checkbox"/>	<input type="checkbox"/>

The diagnosis of occlusion of one or more large intracranial arteries by angio-CT, angio-MR, and/or intra- and extracranial colorDoppler must be obtained at the acute stage in all patients potentially eligible to endovascular treatment (EVT). The addition of advanced neuroimaging studies (perfusional CT or multimodal MRI) is indicated when more than 6 h after the onset of symptoms are elapsed and allows to extend the indications to treatment up to 24 h, in accordance with the inclusion/exclusion criteria used in the DAWN and DEFUSE 3 [5, 6] trials (Tables 10.13 and 10.14).

The choice of EVT should not delay or exclude the IVT when indicated, while the EVT should be started as soon as possible, even

Table 10.13 Inclusion criteria for endovascular treatment between 6 and 16 h (according to the DEFUSE 3 trial) [9]

Inclusion criteria	Yes	No
Age 18–90 years	<input type="checkbox"/>	<input type="checkbox"/>
Occlusion of the intra- and/or extracranial internal carotid artery (ICA) and/or M1 segment of the middle cerebral artery (MCA M1)	<input type="checkbox"/>	<input type="checkbox"/>
mRS pre-stroke 0–2; life expectancy ≥ 6 months	<input type="checkbox"/>	<input type="checkbox"/>
NIHSS ≥ 6	<input type="checkbox"/>	<input type="checkbox"/>
Ischaemic core < 70 ml + penumbra > 15 ml ($T_{\max} > 6$ s) + penumbra/core mismatch $> 1.8^a$	<input type="checkbox"/>	<input type="checkbox"/>

^aCT perfusion or MR DW/PW, using image postprocessing software

Table 10.14 Inclusion criteria for endovascular treatment between 6 and 24 h (according to the DAWN trial) [10]

Inclusion criteria	Yes	No
Age ≥ 18 years	<input type="checkbox"/>	<input type="checkbox"/>
Occlusion of the terminal tract of the internal carotid artery (ICA) and/or M1 segment of the middle cerebral artery (MCA M1)	<input type="checkbox"/>	<input type="checkbox"/>
mRS pre-stroke 0–1; life expectancy ≥ 6 months	<input type="checkbox"/>	<input type="checkbox"/>
NIHSS ≥ 10	<input type="checkbox"/>	<input type="checkbox"/>
Clinical/imaging mismatch ^a : <ul style="list-style-type: none"> • Age ≥ 80 years, NIHSS score ≥ 10, and ischaemic core < 21 ml • Age < 80 years, NIHSS score ≥ 10, and ischaemic core < 31 ml • Age < 80 years, NIHSS score ≥ 20, and ischaemic core < 51 ml 	<input type="checkbox"/>	<input type="checkbox"/>

^aCT perfusion or MR DW/PW, using image postprocessing software

during thrombolytic infusion. In the case of IVT administered in a first level centre and patient eligible for EVT, transport to the reference centre should be carried out as soon as possible in an ambulance with medical personnel on board, without interrupting thrombolytic infusion.

The greatest evidence of EVT efficacy was observed in case of a terminal internal carotid artery occlusion (ICA) and in the M1/M2

segment of the middle cerebral artery (MCA M1/M2) occlusion. Less robust evidence has been observed in the treatment of the more distal branches of the MCA and the anterior cerebral tract A1 (ACA A1). EVT is advised in case of occlusion of the dominant vertebral artery (VA) (VA of greater calibre in an asymmetrical posterior circle, or the only one that supplies the basilar artery), the basilar artery (BA) or the posterior cerebral artery tract P1 (PCA tract P1), although no evidence from randomized trials is at present available. EVT is NOT indicated for non-dominant VA occlusion, postero-inferior cerebellar artery (PICA), antero-inferior cerebellar artery (AICA), superior cerebellar artery (SCA), or distal segments of the PCA occlusion. In case of occlusion of distal or small-calibre branches, which cannot be treated with current thromboaspiration and/or thrombectomy techniques, intrarterial thrombolysis can be considered.

In patients with NIHSS score of 5 or less, EVT should be performed by assessing the risks and benefits of the procedure, particularly in relation to the potential disability of the symptoms. In these cases, EVT should preferably be performed in randomized clinical trials.

EVT in patients with an ASPECT score <6 on plain brain CT or with ischaemic core volume >70 ml on CT perfusion or MRI DW/PW can be considered after risk/benefit assessment, particularly in relation to the patient age, severity and type of neurological deficit, time from onset of symptoms, site of injury, and extent of core/perfusion mismatch.

In case of patient centralization from a first level centre, consider the opportunity to repeat a plain brain CT scan to highlight any worsening of the ASPECT score, especially in the case of long-distance transport.

EVT can also be considered in patients with disabilities prior to stroke (mRS >2); however in these patients it is appropriate to carefully assess the risk/benefit ratio of treatment similarly to that reported in the previous note.

During the EVT and for the following 24 h, it is necessary to maintain pressure values below 180/105 mmHg. Rapid reductions of

pressure values must be avoided during EVT. The choice of the optimal pressure target may be based on the degree of recanalization of the occluded vessel and the possible presence of additional prognostic elements of haemorrhagic transformation and negative outcome.

In patients with stenosis or occlusion of the internal extracranial carotid artery ipsilateral to the intracranial occlusion, it may be necessary to combine EVT with angioplasty treatment with or without possible stent release. There is currently no evidence from randomized trials about the superiority of acute extracranial stenting treatment in these cases. The therapeutic choice must take into account the risk/benefit ratio of the treatment, also in relation to peri- and post-procedural antiplatelet therapy.

Admission to Stroke Unit

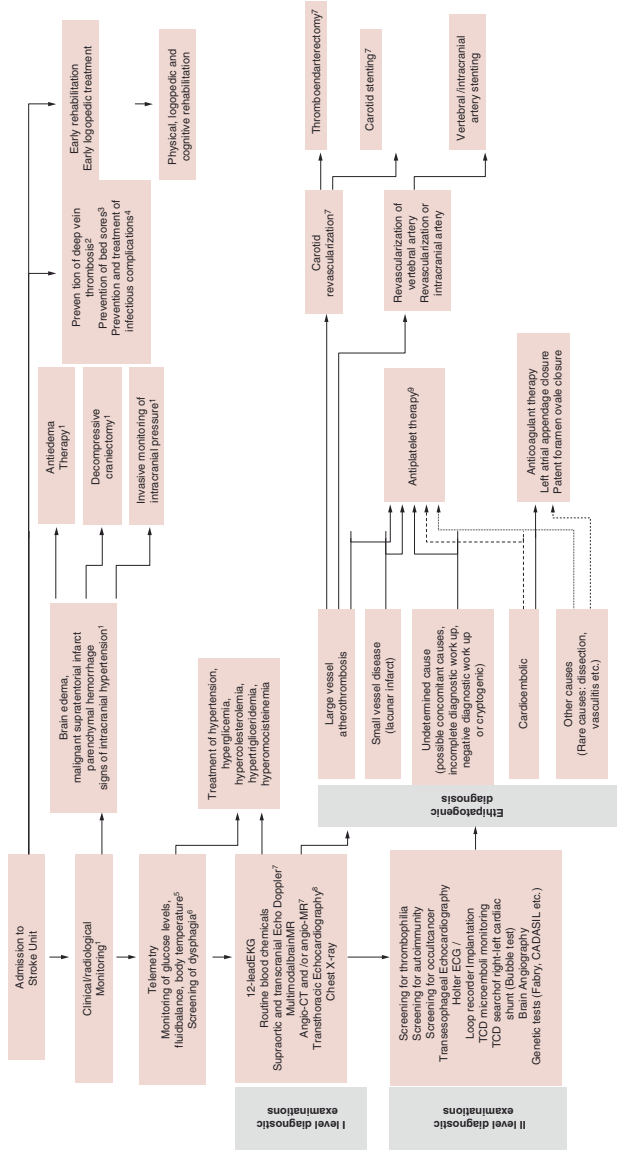
For a detailed description, see the guidelines [2]; in the following list, we refer to the algorithm (Fig. 10.4):

1. Clinical/radiological monitoring in Stroke unit. In case of onset of cerebral oedema related to ischaemic lesion, intravenous administration of osmotic diuretics such as 10% glycerol (1.2 g/kg) or 18% mannitol (0.25–1 g/kg every 4–8 h) is indicated and should be used, if possible, for a period not exceeding 5 days. During therapy with osmotic agents, monitor blood count, renal function, and electrolytes. Furosemide (dose of 10–20 mg) can be added to osmotic diuretic therapy.

In the presence of signs of intracranial hypertension, rapidly deteriorating clinical picture with GCS score <8 and signs of initial transtentorial herniation or hydrocephalus, invasive monitoring of intracranial pressure is indicated. A cerebral perfusion pressure between 50 and 70 mmHg is considered sufficient to maintain brain self-regulation.

In case of clinical and radiological diagnosis of supratentorial malignant cerebral infarction, decompressive hemicraniectomy is indicated within 48 h of stroke onset in previously self-sufficient adult patients under 60 years of age, regardless of the

Figure 10.4 Admission to neurovascular unit



presence of aphasia. After 48 h from the onset of the stroke, surgical decompression is less effective but can still be performed.

In the case of parenchymal haematoma, particularly if associated with increased intracranial pressure and midline shift, refer to the indications in the section 'Patient with Intraparenchymal Haemorrhage'.

In case of complications (symptomatic brain haemorrhage, oral angioedema) after treatment with r-tPA, see section 'Acute Complications of Intravenous Thrombolysis'.

2. Plegic patients with altered consciousness, obese, and/or with previous venous pathology of the lower limbs are at high risk of deep venous thrombosis. In these patients, the use of intermittent pneumatic compression is recommended, as well as adequate mobilization and hydration. The use of prophylactic heparin is recommended as a drug therapy (non-fractional heparin 5000 IU \times 2 or low-molecular-weight heparin in the recommended prophylactic dosage for the individual molecules: dalteparin 5000 IU/day, enoxaparin 4000 IU/day, nadroparin 3800 IU/day). Heparin therapy should be initiated in ischaemic stroke at the time of hospitalization and in haemorrhagic stroke between day 1 and day 4 from onset but not in the case of active bleeding.
3. Bedsores are a severe complication of acute stroke, associated with increased mortality and worse clinical outcome. Prevention of bedsores is based on early mobilization, avoiding the rubbing that occurs during the movements of the patient, the use of foam, air, gel, or water mattresses, avoiding direct and prolonged pressure on skin areas even with the use of pillows, a diet rich in proteins and calories, skin care, and protection with careful daily inspection, frequent cleaning (avoiding moisture and subsequent maceration), and use of protective creams.
4. Urinary tract infection, closely associated with catheterization and its duration, is the most common infectious complication in patients with acute stroke. Infectious pneumonia, particularly aspiration or *ab ingestis* pneumonia, is the second most frequent infectious complication in patients with acute stroke.
5. Oxygen administration is indicated in patients with $\text{SaO}_2 < 94\%$; correction of hyperthermia is indicated, preferably with

paracetamol, keeping the temperature below 37 °C; correction of hyperglycaemia with subcutaneous or intravenous insulin (according to individual need) is indicated in patients with glycaemia >180 mg/dl.

6. Dysphagia is a frequent consequence of stroke with negative effects on clinical and functional outcome, prolonged hospitalization and increased mortality. A standardized clinical assessment of the risk of dysphagia (using the BSA: Bedside Swallowing Assessment) and a simple test, such as the water swallowing test, are recommended in all patients with acute stroke.
7. All patients with an acute cerebrovascular event, especially those who are not submitted to acute CT-angiography or MR-angiography, should undergo an evaluation of the extra- and intracranial vessels, in particular with echocolorDoppler of the supraortic trunks and transcranial colorDoppler, as soon as possible.

The investigations carried out can highlight different types of carotid disease:

- Absence of extracranial steno-occlusive disease or presence of noncomplicated plaques with stenosis <50% (NASCET method) [7]: no further interventions
- Extracranial steno-occlusive disease with stenosis >50% (NASCET method) [7] or unstable carotid plaque congruous with the territory of the stroke or with the symptoms presented by the patient: request vascular surgical consultation for carotid endoarterectomy (CEA) or stenting for secondary prevention
- Extra- and/or intracranial artery dissection, multiple dissections
- Extra- and/or intracranial artery occlusion

CEA or stenting must be performed between 48 h and 14 days after the acute event, taking into account patient comorbidities and the extent of the ischaemic lesion or the presence of any haemorrhagic infarction.

NB. Effectiveness and safety of carotid revascularization in emergency (within 48 h) were not proven by randomized controlled trials. The possibility of emergency or urgent treatment could be considered in case of acute stroke with small ischaemic core and large area of penumbra due to haemodynamic

effect of carotid stenosis/occlusion or in case of onset of neurological deficit due to acute thrombosis of the surgical site or stent during elective surgery.

8. Transthoracic echocardiogram allows a better definition of the etiopathogenetic subtypes, also highlighting the possible degree of systolic dysfunction of the ventricles, the state of the pericardium, possible valvular pathologies, possible thrombosis at the apex of the left ventricle, or the presence of an idiopathic and/or secondary dilated cardiomyopathy.

Transoesophageal echocardiogram should be reserved for the study of the interatrial septum in the case of patent foramen ovale and for the search of aortic arch plaques, the possible presence of aortic arch dissection, cardiac masses (e.g. atrial myxoma), or infectious endocarditis.

9. Secondary prevention therapy with acetylsalicylic acid or clopidogrel should be initiated in all patients as soon as possible, unless contraindicated. In the patient undergoing IVT, the administration of antiplatelet drugs should be postponed to 24 h after the start of treatment and after cerebral neuroimaging control for any bleeding.

In patients with mild stroke (NIHSS ≤ 4) or TIA at high risk of recurrence (ABCD2 > 3 , see below), the initiation of a dual antiplatelet therapy is indicated. This therapy should be continued for no longer than 30 days, except in special cases (e.g. intracranial stenosis), due to unfavourable risk/benefit ratio of more prolonged treatments.

In patients with extracranial arterial dissection, there is no evidence of superiority between the use of antiplatelet and anticoagulants in the acute phase. In case of intracranial dissection, it would be preferable not to administer anticoagulants because of the potential risk of SAH in case of vessel rupture.

Transient Ischaemic Attack

There are currently two definitions of Transient Ischaemic Attack (TIA): a transient focal neurological deficit lasting less than 24 hours irrespective of neuroimages (clinical definition), and a transient neurological deficit lasting less than 24 hours with no evidence of ischaemic lesions on neuroimaging (tissue based definition).

Table 10.15 Symptoms that, if present in isolation, do not allow the diagnosis of TIA

-
- Loss of consciousness
 - Feeling of instability
 - Generalized asthenia
 - Mental confusion
 - Loss/reduction of vision associated with reduced level of consciousness
 - Incontinence of faeces and urines
 - Vertigo
 - Diplopia
 - Dysphagia
 - Loss of balance
 - Acouphenes
 - Sensory symptoms confined to a part of a limb or face
 - Scintillating scotomas
 - Amnesia
 - Drop attack (sudden fall to the ground in the absence of loss of consciousness)
-

The crescendo TIA is characterized by two or more episodes referable to transient ischaemic attacks within 24 h (complete resolution of symptoms between events is required). It requires differential diagnosis with *capsular* and *pontine warning syndrome*, epileptic seizures, and *amyloid spells* from amyloid angiopathy (Table 10.15).

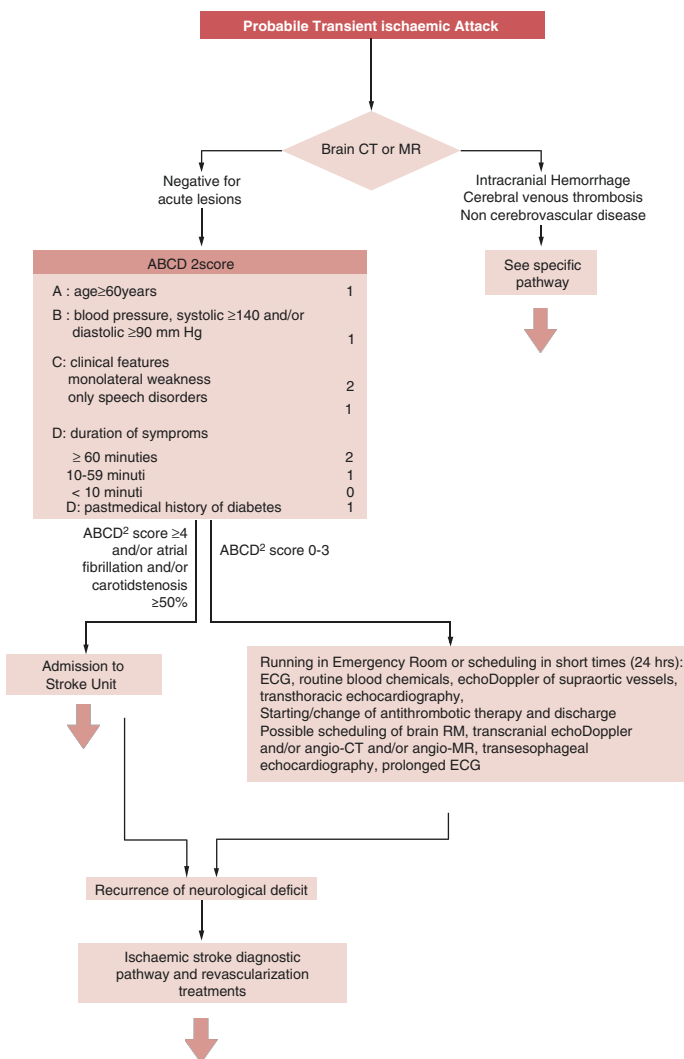
TIA algorithm is shown in Fig. 10.5; for a detailed description, refer to the guidelines [2].

The ABCD2 score, obtained by adding the scores of the individual items age, blood pressure, clinical picture, duration of symptoms, and diabetes, predicts the risk of stroke in the next 48 h in patients with transient ischaemic attack [8]. The risk is stratified into:

- Low (score <4)
- Moderate (score 4–5)
- High (score >5)

However, regardless of the ABCD2 score, the presence of atrial fibrillation or haemodynamically significant carotid stenosis requires admission to Stroke unit. In addition, hospitalization is

Figure 10.5 Algorithm for TIA



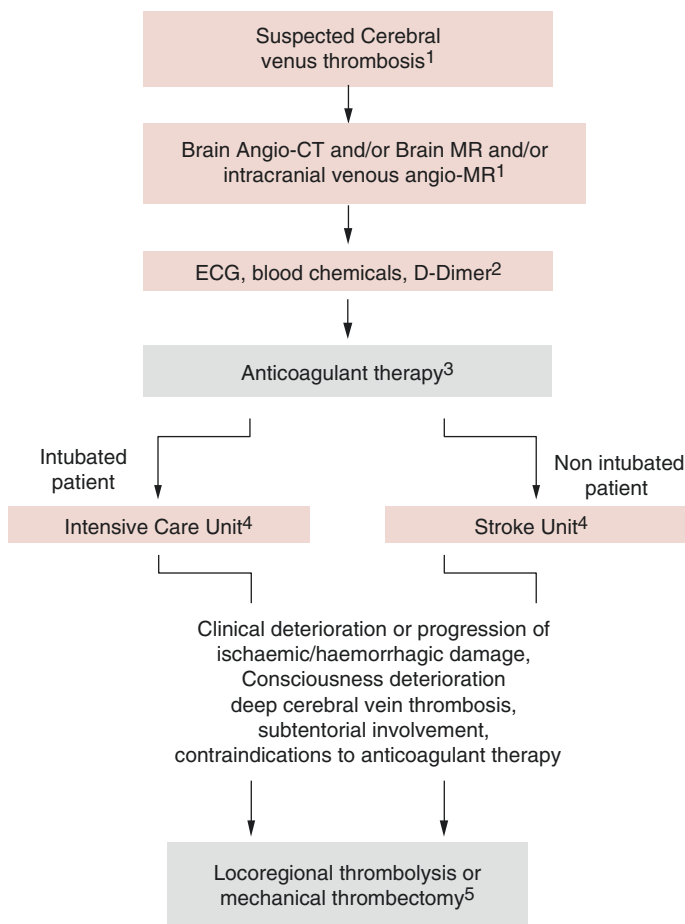
strongly recommended even in the presence of crescendo or recurrent TIA, symptomatic intracranial stenosis $\geq 50\%$, dissection of the supraortic or intracranial trunks, or impossibility to perform the necessary investigations in a short time outside the hospital.

In the presence of a dedicated TIA Clinic with immediate access to instrumental examinations for patients with TIA, all patients, regardless of the ABCD2 score, can be managed outside the Stroke unit.

Patient with Suspected Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) algorithm is shown in Fig. 10.6, with the description of the different steps; for a detailed description, please refer to the guidelines [2, 9].

1. Clinical suspicion of cerebral venous thrombosis arises when the focal neurological deficit is preceded by headache in the previous days, and there are epileptic seizures at the onset (focal with/without secondary generalization). In these circumstances, differential diagnosis with PRES and RCVS is required: the radiological picture in MR/angio-MR or in CT/angio-CT can help in differential diagnosis. Cerebral CT can show an ischaemic lesion, frequently with haemorrhagic transformation, with atypical localization for an arterial territory; sometimes it is possible to show signs of thrombosis of a large vein or venous sinus with spontaneously hyperdense image at characteristic sites. Angio-CT allows the identification of site of thrombosis and confirms the diagnosis. Brain MRI can detect ischaemic lesions (DW sequences), the presence of even small infarctions (gradient-echo or T2' sequences) and/or the presence of thrombus with an increase in the endoluminal signal (T1 sequences) [10]. Intracranial venous angio-MR allows the identification of site of thrombosis and confirms the diagnosis (always consider frequent sinus hypoplasia).
2. D-dimer measurement is recommended for suspected cerebral venous thrombosis. D-dimer increase has a high negative predictive value except for patients with cerebral venous thrombo-

Figure 10.6 **Algorithm for cerebral venous thrombosis**

sis with headache as the only symptom and without evidence of parenchymal lesions. D-dimer determination is not a validated test in pediatric age.

3. In patients with cerebral venous thrombosis without contraindication to heparin therapy, treatment with subcutaneous low-

molecular-weight heparin (LMWH) at anticoagulant dose or with intravenous non-fractional heparin with aPTT monitoring (which should be at least doubled) is indicated, as well as hospitalization in Stroke unit.

The use of LMWH is preferable to intravenous non-fractional heparin, except in cases of contraindications or when a rapid reversal of the anticoagulant effect may be necessary. Intraparenchymal haemorrhage and SAH, possibly concomitant with cerebral venous thrombosis, are not a contraindication to anticoagulant treatment.

From the first days of therapy, it is indicated to emigrate to heparin therapy the oral anticoagulant therapy with antivitamin K drug, to be continued for at least 3 months in cases due to a transient or modifiable risk factor and for 6–12 months in patients with idiopathic forms or with minor degree hereditary thrombophilia. Anticoagulant therapy of indefinite duration should be performed in patients with two or more episodes of idiopathic cerebral venous thrombosis or in patients in whom venous thrombosis is associated with severe hereditary thrombophilia (antithrombin III deficiency, homozygous mutation of factor V Leiden, or two or more associated thrombophilic conditions). The use of direct oral anticoagulants is not indicated, especially in the acute phase.

4. In patients with cerebral venous thrombosis and signs of endocranial hypertension, it is advisable to keep the head of the bed at 30°, hyperventilate the patient with the aim of maintaining PaCO₂ value between 30 and 35 mmHg, correct any hyperthermia and hypoxemia, and administer intravenous osmotic diuretics. In patients with a high risk of cerebral herniation, ventriculostomy and decompressive craniectomy may be considered. Early surgery (within 12 h of hospitalization) and young age are predictive factors for favourable outcome.

Steroids are NOT recommended in patients with cerebral venous thrombosis as they may aggravate the thrombotic process and the clinical picture. Exceptions are conditions in which the steroid is indicated for the treatment of a specific disease leading to venous thrombosis such as chronic inflammatory diseases in the active phase and Behçet's disease.

In patients with cerebral venous thrombosis, the administration of acetazolamide is NOT recommended.

The use of antiepileptic drugs is indicated in cases of cerebral venous thrombosis with supratentorial lesions and epileptic seizures.

5. In patients with clinical deterioration or progression of venous infarction and/or parenchymal haemorrhage despite heparin therapy, reduced alertness and coma, deep cerebral venous thrombosis, subtentorial involvement, or major contraindications to anticoagulant therapy (haemorrhagic diathesis, thrombocytopenia $<100 \times 10^9/l$, recent gastrointestinal haemorrhage), locoregional thrombolytic therapy, and/or mechanical thrombectomy are indicated in experienced centres. However, the treatment modalities are not standardized, as is the minimum duration of the systemic anticoagulant treatment before it is considered unsuccessful.

In the case of extended thrombosis, following initial local administration of thrombolytic, a continuous infusion (e.g. alteplase 1–2 mg/h) can be performed by micro catheter for 12–24 h, then repeating the angiographic examination to verify its effectiveness.

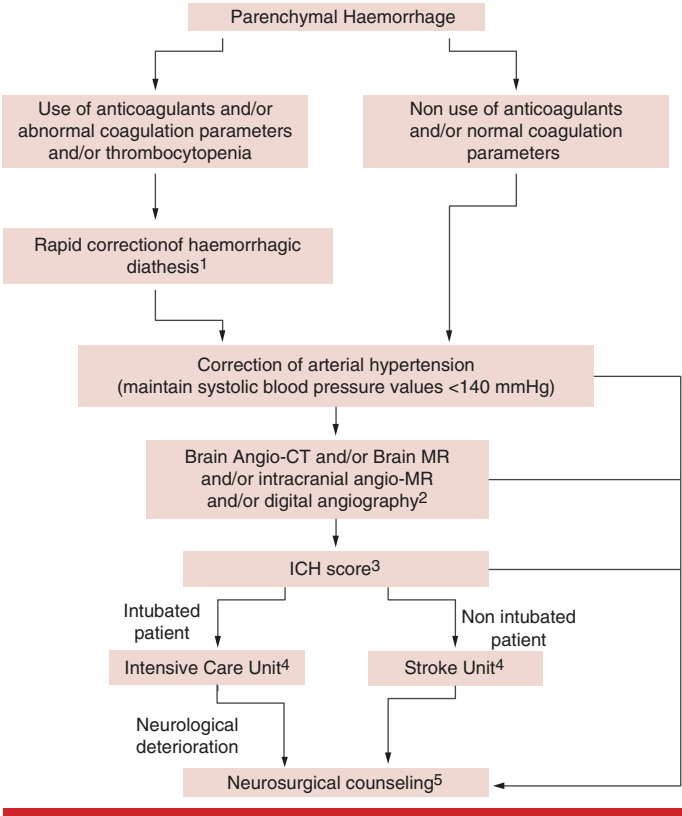
Before and after endovascular treatment, adequate anticoagulation of the patient should be guaranteed to prevent reocclusion of the vessel [11].

Patient with Intraparenchymal Haemorrhage

Intraparenchymal haemorrhage algorithm is shown in Fig. 10.7, with the description of the different steps; for a detailed description, please refer to the guidelines [2].

1. Correction of haemorrhagic diathesis in relation to the type of antithrombotic drug used and/or to the alteration of the coagulative profile and/or thrombocytopenia (Table 10.16).
2. Diagnostic investigations such as intracranial CT-angiography, brain MR with MR intracranial arterial and venous angiography, and/or digital angiography are indicated: in patients with atypical brain haemorrhage, in the absence of a clear aetiology of bleeding (especially if young and without hypertension), if brain CT suggests the presence of a structural lesion underlying the haemorrhage, and in patients who are candidates for surgical treatment.

Figure 10.7 **Algorithm for intraparenchymal haemorrhage**



MR and angio-MR are particularly useful in selected patients, especially in suspected amyloid angiopathy and, at least 30 days after the event, in patients with lobar lesions without amyloid angiopathy and with negative angiography, for the diagnosis of any cavernous angiomas of surgical competence.

- 3. Computing of the ICH score (Table 10.17 and Fig. 10.8).
- 4. Admission and management of patients with intracerebral haemorrhage in Stroke unit (Table 10.18).

Table 10.16 Correction of haemorrhagic diathesis in case of cerebral haemorrhage [12]

In case of cerebral haemorrhage

- Check the use of anticoagulant drugs and the time of the last intake (for direct oral anticoagulants check renal and liver function).
 - Adequate intravenous hydration.
 - Blood transfusion, if necessary.
 - Fresh frozen plasma (to be used as plasma expander and not as pro-coagulating agent; 15–20 ml/kg).
 - Tranexamic acid (as an adjuvant; 1 g possibly repeatable every 6 h if necessary).
 - Desmopressin (in selected cases of coagulopathy; 0.3 mg/kg in iv infusion, maximum dose 20 mg).
-

In case of cerebral haemorrhage during treatment with antivitamin K anticoagulants, stop anticoagulant medication and administer:

- **Vitamin K** (10 mg by slow intravenous infusion in 5 min, repeatable after 12 h if coagulation is still not normal).
 - **Prothrombin complex concentrates** (PCCs): if INR 2–3, give 9–25 U/kg factor IX; if INR 4–6, give 35 U/kg factor IX; if INR >6, give 50 U/kg factor IX.
-

In case of cerebral haemorrhage during dabigatran therapy, stop anticoagulant medication and administer:

- **Idarucizumab** 2.5 g as an iv bolus and additional 2.5 g iv after 15 min. If idarucizumab is not available, administer:
 - **Active carbon** (within 2–3 h)
 - **Prothrombin complex concentrates** (PCC) 50 U/kg (25 U/kg additional if necessary)
 - **Activated prothrombin complex concentrate** (FEIBA®) 50 U/kg (maximum 200 U/kg/day)
 - Haemodialysis: in emergency
-

In case of cerebral haemorrhage during treatment with anti-factor X anticoagulants, stop anticoagulant medication and administer:

- **Andexanet alpha** (approved for apixaban or rivaroxaban; not yet available in Italy). If andexanet alpha is not available, administer:
 - **Active carbon** (within 2–3 h of last intake of anticoagulant)
 - **Prothrombin complex concentrate** (PCC) 50 U/kg (25 U/kg additional if necessary)
 - **Activated prothrombin complex concentrate** (FEIBA®) 50 U/kg (maximum 200 U/kg/day)
-

In case of cerebral haemorrhage during intravenous heparin therapy, stop anticoagulant medication and administer:

- **Protamine sulfate** at varying doses depending on the time of discontinuation of therapy (typically 1 mg per 100 U of administered heparin)
-

In case of cerebral haemorrhage and thrombocytopenia (<60.000/l), administer:

- Platelet concentrates
-

Table 10.17 ICH score [13]

	ICH score
Score at Glasgow Coma Scale	
3–4	2
5–12	1
13–15	0
Bleeding volume (ml)	
>30	1
<30	0
Intraventricular haemorrhage	
Yes	1
No	0
Infratentorial haemorrhage	
Yes	1
No	0
Age (years)	
>80	1
<80	0

Glasgow Coma Scale (GCS) score: indicates the initial GCS score at patient arrival or after cardiopulmonary resuscitation; haemorrhage volume: volume at initial CT, calculated using the $A*B*C/2$ method

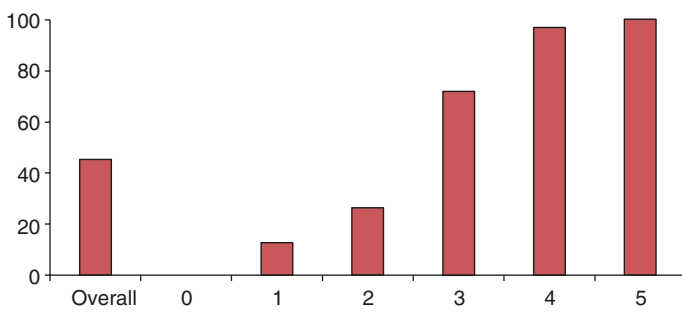
Figure 10.8 30-day mortality according to ICH score

Table 10.18 Management of the patient with acute intracerebral haemorrhage

-
- Management of patients with acute intracerebral haemorrhage in dedicated facilities (Stroke units) has been shown to reduce mortality and disability.
 - Treatment of blood pressure is indicated, to reach systolic blood pressure ≤ 140 in about an hour and maintain it for the following days.
 - Antiepileptic prophylaxis is not indicated, while treatment of epileptic seizures is indicated.
 - For the prophylaxis of deep venous thrombosis, the use of elastic graduated compression stockings is not recommended. Gradual intermittent compression devices are recommended as an alternative to medical treatment if this is considered at risk. After 4–5 days from the onset of cerebral haemorrhage, depending on the extent and evolution of bleeding, the use of low-molecular-weight heparin or non-fractional heparin at prophylactic doses may be considered.
 - For the treatment of intracranial hypertension, the following options are indicated:
 - **Osmotic agents:** 10% glycerol (1.2 g/kg) or 18% mannitol (0.25–1 g/kg every 4–8 h) in case of severe intracranial hypertension, rapidly deteriorating clinical condition, oedema surrounding the haemorrhage. For the known rebound phenomena, it is to be used for less than 5 days. During therapy with osmotic agents, monitor blood count, renal function, electrolytes, and plasma osmolality.
 - **Furosemide:** at a dose of 10–20 mg, administered simultaneously with osmotic therapy.
 - **Hyperventilation:** constant ventilation with volumes of 12–14 ml/kg with pCO_2 reduction targets at 30–35 mm Hg (25–30% intracranial pressure reduction).
 - **Sedation and curarization:** Neuromuscular paralysis in combination with adequate thiopental sedation prevents elevations of intrathoracic pressure from vomiting, coughing, and resistance to mechanical ventilation. In these situations, non-depolarizing drugs such as veturonium or pancuronium are preferred.
 - **Invasive monitoring of intracranial pressure** in selected cases (patients with GCS ≤ 8 and clinical evidence of initial transtentorial herniation or significant hydrocephalus). Cerebral perfusion pressure between 50 and 70 mmHg is considered sufficient to maintain brain self-regulation.
 - Steroid use is NOT indicated.
-

Table 10.19 Surgical treatment of cerebral haemorrhage

-
- It is recommended for patients with cerebellar haematoma larger than 3 cm who have clinical neurological deterioration, brainstem compression, and/or hydrocephalus due to IV ventricle obstruction.
 - Decompressive craniectomy can be considered in case of superficial haematomas with a depth of less than 1 cm from the cerebral cortex, whereas it is not indicated in the case of nonsuperficial intracerebral haematomas. The treatment is to be considered only as life-saving, in young patients with progressive clinical deterioration, who have not benefited from treatments aimed at reducing intracranial pressure.
 - It is indicated for intracerebral haemorrhages associated with aneurysms or arteriovenous malformations, if the associated structural lesion is surgically accessible.
 - It is indicated in case of hydrocephalus secondary to intraventricular haemorrhage with clinical deterioration.
 - It is not indicated as a routine early intervention regardless of the surgical technique, except in the case of neurological deterioration.
 - It is not indicated for small intracerebral haemorrhages (<10 cm) or^a minimal deficits.
 - It is not indicated for intracerebral haemorrhages with GCS ≤ 4 due to high mortality and extremely poor neurological outcome.
 - It is not indicated for intracerebral haemorrhages associated with aneurysms or arteriovenous malformations, if the associated structural lesion is not surgically accessible.
-

^aCorrection of haemorrhagic diathesis in relation to the type of antithrombotic drug used and/or to the alteration of the coagulative profile and/or thrombocytopenia (see Table 10.16)

5. Indications and contraindications for surgical treatment of cerebral haemorrhage (Table 10.19).

Subarachnoid Haemorrhage

Subarachnoid haemorrhage algorithm is shown in Fig. 10.9, with the description of the different steps; for a detailed description, please refer to the guidelines [2].

Figure 10.9 Algorithm for subarachnoid haemorrhage

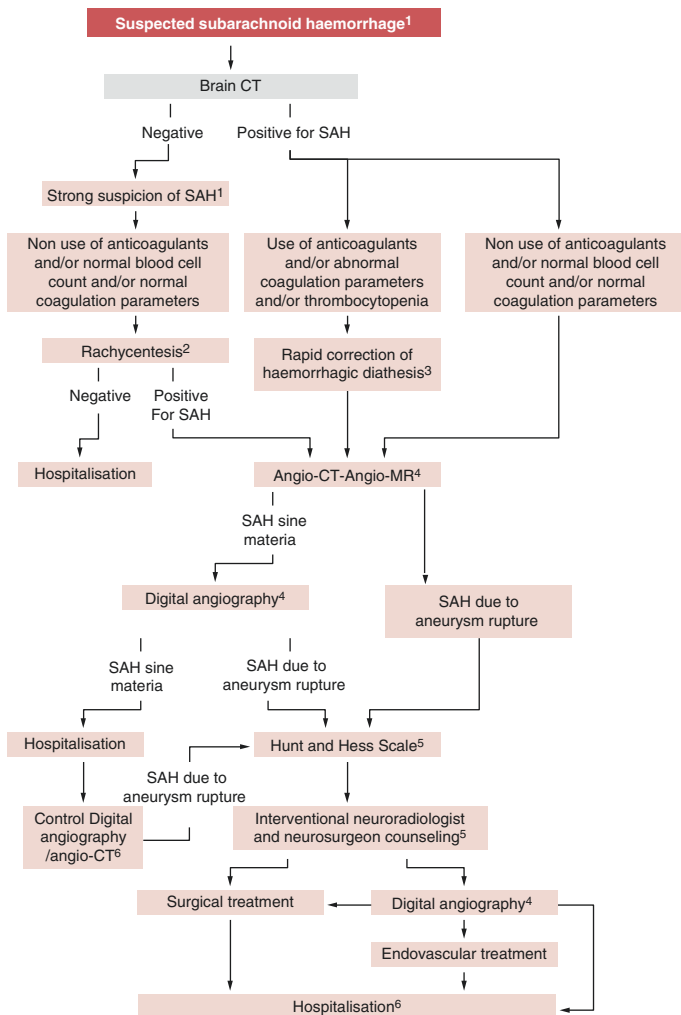


Table 10.20 Criteria for clinical suspicion of SAH

Headache (see also Chap. 5):

- Sudden, violent onset, which reaches its maximum intensity in a short time ('thunderclap headache')
- 'Worst headache in life'
- Sometimes preceded by 'sentinel headache' in the previous days
- Different from the usual attacks of headache in a cephalalgic patient
- New headache in a non-cephalalgic patient
- Onset immediately after or during physical exertion

Accompanied by sensory alterations or loss of consciousness (see Chap. 1)

Signs of meningeal irritation (nuchal rigidity, Brudzinski's sign, Kernig's sign, nausea and vomiting, photophobia, etc.)

Focal neurological signs (in 2/3 of patients):

- Hemiparesis
 - Paralysis of the III or VI cranial nerve
-

1. Clinical suspicion of subarachnoid haemorrhage (SAH, Table 10.20).
2. **Plain brain CT** is indicated for the emergency diagnosis of SAH, and in the first days of the acute event has a sensitivity close to 100%. However, in the presence of negative brain CT and strong clinical suspicion of SAH, lumbar puncture is indicated. The presence of red blood cells in the CSF is an indicator of recent bleeding but may be difficult to distinguish from the bleeding related to the possible trauma of the procedure, in which case it is useful to consider the gradually reduced number of blood counts in subsequent tubes (index of bleeding from traumatic puncture) and the presence of xanthochromia after centrifugation, a reproducible method to verify the presence of SAH even several days after the disappearance of headache. Xanthochromia is the yellowish colouration of CSF which is due to the degradation of haemoglobin into bilirubin and occurs approximately starting from 12 h after bleeding.

Table 10.21 Hunt-Hess Scale [14]

		Survival %
Grade 0	Silent aneurysm	
Grade I	Asymptomatic or mild headache and minor nuchal rigidity	70
Grade Ia	Focal neurological deficits in the absence of meningeal signs	
Grade II	Cranial nerve deficit, moderate-to-severe headache, nuchal rigidity	60
Grade III	Confusion/drowsiness, mild focal neurological deficits	50
Grade IV	Stupor, moderate hemiparesis	40
Grade V	Coma, decerebrate posturing	10

3. CT-angiography represents the fastest and most sensitive examination for the diagnosis of SAH due to cerebral aneurysm rupture. Digital angiography is the gold standard for the morphological description of the aneurysm and for possible endovascular treatment.
MR-angiography is always indicated when CT-angiography or digital angiography cannot be performed.
4. Treatment of the patient with subarachnoid haemorrhage due to cerebral aneurysm rupture (Tables 10.21 and 10.22).
5. Management and monitoring of patients with subarachnoid haemorrhage (Tables 10.23 and 10.24).

Other Causes of Focal Neurological Deficit

- Subdural haematoma: review history for head trauma, even modest, in the previous 30–40 days, and for any neurological symptoms prior to the onset of focal deficit. Therapy: evaluate neurosurgical indication.
- Epidural haematoma: recent head trauma, possible biphasic course—trauma, loss of consciousness, improvement, and sub-acute worsening after a few hours with progressive focal signs

Table 10.22 Management and monitoring of patient with SAH

-
- Treatment of SAH due to aneurysm rupture by endovascular or surgical intervention is indicated within 72 h of onset.
 - In relation to the Hunt and Hess scale score:
 - Grade I–III: generally associated with a positive outcome; these patients are candidates for early surgery.
 - Grades IV and V: indicative of unfavourable prognosis; these patients need stabilization and to reach grade III to undergo surgery.
 - In patients with SAH who are young and/or with low degrees of clinical severity, with no specific indication and operating conditions, the choice between surgical and endovascular therapy is left to the collaboration between interventional neuroradiologist and neurosurgeon and is influenced by the relative experience of the operators.
 - Advanced age, intermediate, and high clinical grades (3–4 on the Hunt and Hess scale) and in particular aneurysms of the posterior circulation that are difficult to access surgically, regardless of whether they are ruptured or not, are variables that guide the therapeutic choice in favour of an endovascular operation.
 - Surgical treatment of aneurysms with SAH is indicated when, due to aneurysm morphology, anatomical relations, or general vascular conditions, endovascular treatment cannot be performed, and in cases of cerebral aneurysms associated with a haematoma with cerebral compression.
 - Aneurysms of the exclusively intracavernous tract, without erosion of the sphenoid sinus wall, should be considered separately, as they have a low risk of bleeding even if symptomatic. The operation may be necessary because of the presence of compression symptoms rather than the risk of bleeding.
 - The elements in favour of treating an unruptured aneurysm are as follows:
 - Young age (long-life expectancy with increased cumulative risk of aneurysm rupture)
 - Previous SAH from another aneurysm
 - Family history of SAH and/or aneurysms
 - Presence of uncontrolled hypertension
 - Need for anticoagulant treatment
 - Diameter greater than 7 mm
 - Compressive symptoms or evidence of progressive aneurysm increase
 - Location on the midline (anterior communicating or basilar artery aneurysm)
 - Irregular shape
 - In the case of acute hydrocephalus after SAH with reduction of the level of consciousness, treatment with ventricular derivation is indicated, although this increases the risk of bleeding and infectious complications.
-

Table 10.23 Management and monitoring of patient with SAH

-
- Neurological monitoring
 - Support for vital functions
 - Check blood tests and glucose values
 - Treatment of hyperthermia
 - Analgesic therapy
 - Use of intermittent compression devices for the lower limbs to prevent deep vein thrombosis in bedridden patients
-
- In case of SAH from cerebral aneurysm rupture and inability to treat it, treatment with tranexamic acid for a maximum of 72 h is recommended
-
- Up to 24% of all SAH patients with a first negative angiographic examination show the presence of a cerebral aneurysm on a second angiographic examination. The percentage increases to 49% excluding patients with perimesencephalic SAH and negative baseline brain CT
 - The timing for the repetition of a second diagnostic examination in case of SAH with initial negative angiography should be based on the general condition of the patient and the presence of complications. A series of cases show a time between 4 days and 4 weeks
 - A third angiographic examination at 2–3 months may be useful in selected cases
-
- In case of perimesencephalic subarachnoid haemorrhage at brain CT, the possibility of detecting an aneurysm on angiographic examination varies between 2% and 9%
 - The diagnostic sensitivity of brain CT for subarachnoid perimesencephalic haemorrhage is reduced after 48–72 h from the onset of symptoms
 - Remote repetition of the angiographic or CT-angiography examination should be performed in the patient with perimesencephalic subarachnoid haemorrhage and a first negative angiography, in case of strong suspicion of aneurysm (e.g. presence of cerebral vasospasm) or nonoptimal technical quality of the first angiographic examination
-

often followed by signs of general brain suffering. Therapy: evaluate neurosurgical indication (see Chap. 12).

- Brain neoplasms. Therapy: evaluate neurosurgical indication.
- Brain abscess, encephalitis, and demyelinating disease. Therapy: see specific chapters.

Table 10.24 Vasospasm in case of subarachnoid haemorrhage**Vasospasm in case of SAH**

- Vasospasm of the cerebral arteries during SAH commonly appears from day 7 to day 21 after onset and may be responsible for late ischaemia.
- Transcranial Doppler (TCD) is indicated for the diagnosis and monitoring of vasospasm.
- Oral administration of nimodipine (60 mg every 4 h) is indicated for the prevention and treatment of vasospasm after SAH and should be continued until the 21st day after onset. If oral administration is not possible, iv administration with careful control of blood pressure may be indicated.
- Therapeutic hypertension is useful in patients with vasospasm and secondary cerebral ischaemia, unless there are cardiovascular or neurological contraindications.
- Hypervolemia and haemodilution, statins, and magnesium sulphate may be useful for the prevention and treatment of vasospasm, but their effectiveness has not been univocally demonstrated.
- Intraarterial treatment with nimodipine and/or endovascular angioplasty is indicated for patients with vasospasm after SAH, for whom first-line treatment has been shown to be ineffective.

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11. Para- and Tetraplegia in the Emergency Room and in the Intensive Care Unit

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Introduction

Para-/tetraplegia can be a consequence of a heterogeneous group of spinal cord pathologies. Clinical features depend on the level of the injury along the spinal cord. Spinal cord syndromes are typically

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featured by acute or subacute loss or damage of the following functions:

- Motor (“sublesional” motor impairment: motor function is damaged below the level of the spinal injury)
- Sensory (“sublesional” sensory impairment, also known as “sensory level”)
- Vegetative: bladder dysfunction (both retention or incontinence can occur) and rectal dysfunction, with or without altered perineal sensitivity

A complete spinal cord syndrome is easily recognizable; however, but not always, especially at onset, the involvement of the three systems can be asymmetrical, thus misleading the assessment. Table 11.1 shows different types of clinical presentation, based on the extent of the spinal lesion on the transverse plane (transverse syndromes are due to the complete interruption of the spinal cord; segmentary/incomplete syndromes due to its incomplete interruption, with a prominent involvement of the gray or the white matter, respectively).

The differential diagnosis is actually broad. The accurate knowledge of the anatomy and the vascular supply of the spinal cord can help discriminating between the different forms of acute myelopathy, which can be essentially classified into four major etiologies: infectious/inflammatory, extrinsic compression, vascular disorders, and post-traumatic. About 10–20% of cases are referred as “idiopathic myelopathy” because of the impossibility of determine the etiology.

Acute spinal cord syndromes represent one of the most critical neurological emergencies. In this chapter, we review the *diagnostic algorithm* and the *therapeutic algorithm*. Making a prompt diagnosis is fundamental, since early treatment influences prognosis, both in cases requiring neurosurgery and in cases requiring “simple” medical treatment. Hence, the importance of recognizing clinical features pointing to perform an urgent MRI of the spine (ideally, an imaging of the entire spinal cord), also in the Emergency Department setting.

Table 11.1 Clinical manifestations of acute para-/tetraplegia due to spinal cord injury (depending on the location of the injury in the transverse plane)

Type of injury	Involvement of spinal tracts	Clinical signs	Examples/most common etiologies
Complete	All	Under the injury <ul style="list-style-type: none"> Pyramidal/motor Sensory Vegetative 	<ul style="list-style-type: none"> Trauma with or without vertebral fracture Extrinsic compression Transverse myelitis (viral or postinfectious)
Brown-Sequard syndrome	Hemisecion of spinal cord <ul style="list-style-type: none"> Ipsilateral corticospinal tract Ipsilateral posterior cord Contralateral spinothalamic tract 	<ul style="list-style-type: none"> Ipsilateral: motor + proprioception impairment (directly under the lesion) Contralateral thermic and pinprick sensitivity impairment (two segments under the lesion) 	<ul style="list-style-type: none"> Demyelinating disease Compression Post-traumatic (usually with a good prognosis)
Anterior spinal cord syndrome	<ul style="list-style-type: none"> Bilateral ventral horns Spinothalamic Tract Autonomic Fibers 	Under the injury <ul style="list-style-type: none"> Bilateral flaccid paralysis Thermic and pain anesthesia Sphincterial dysfunction Proprioception and touch sensation are preserved 	<ul style="list-style-type: none"> Occlusion of anterior spinal artery Trauma (from flexion, with dislocation of vertebral body fragment) Infection with West Nile virus
Posterior cord syndrome	Bilateral posterior cord	Under the lesion bilateral loss of touch, vibration, and proprioceptive sensation, potentially resulting in sensory ataxia	Rare <ul style="list-style-type: none"> Vitamin B12 deficiency (usually chronic) Copper deficiency (usually chronic)

Continued

Table 11.1 Continued

Type of injury	Involvement of spinal tracts	Clinical signs	Examples/most common etiologies
Central cord syndrome	<ul style="list-style-type: none"> • Spinothalamic tract • Corticospinal tract • Autonomic fibers 	<ul style="list-style-type: none"> • Dissociated sensory impairment: loss of pain and temperature sensation, preservation of vibration, and proprioceptive sensation) • Motor impairment especially in the upper limbs (if cervical localization) • Vegetative dysfunction 	<ul style="list-style-type: none"> • Syringomyelia • Optic neuromyelitis • Trauma: it is the most frequent post-traumatic syndrome. It is often due to the abrupt hyperextension of the neck, thus producing cervical myelopathy, with major involvement of the upper limbs, resulting in motor loss, hyperesthesia, and transient autonomic dysfunction. Good prognosis with a 75% chance of complete recovery
Conus medullaris syndrome	<ul style="list-style-type: none"> • Autonomic fibers • Sacral segments 	<ul style="list-style-type: none"> • Sphincterial dysfunction • Saddle anesthesia • Limited motor impairment • Rarely, pain 	<ul style="list-style-type: none"> • Post-viral myelitis • Trauma with vertebral fracture between T11 and L1
Cauda equina syndrome	Cauda spinal segments	<ul style="list-style-type: none"> • Floppy paralysis (early and often asymmetrical) • Radicular hypoesthesia • Sphincterial dysfunction 	<ul style="list-style-type: none"> • Viral polyradiculitis (e.g., CMV) • Extrinsic compression • Trauma with vertebral fracture under L1/L2
Segmental myelopathies	Selective involvement of a tract (on the vertical plane)	Selective anterior/posterior cord involvement	Usually due to chronic metabolic or degenerative conditions (e.g., B12 deficiency), less frequently can be paraneoplastic; occasionally due to acute demyelination (especially affecting the posterior cord, with an acute, isolated proprioceptive sensation loss)

In the context of Intensive Care, neurologists may be called to evaluate another serious clinical condition presenting with para-/tetraplegia. This disease is labeled as Intensive Care Unit Acquired Weakness (ICUAW); usually, the neurological damage is due not to any spinal cord injury, but to a peripheral disease involving nerves or muscles or both. In addition to the difficult differential diagnosis, the approach in these cases is complicated by the context (patient are often unable to cooperate, intubated, sedated, with systemic/post-traumatic comorbidities) and by the difficulty in defining the onset and progression of weakness (which is often randomly detected while attempting to extubate). Medical history must be carefully collected by relatives, pointing to investigate any risk factor and condition occurring prior to hospitalization (preexisting motor impairments, recent infections, insect bites, family diseases, use of drugs or substances, and cognitive decline) and ongoing treatments.

Table 11.2 lists the causes of nontraumatic acute myelopathy. The differential diagnosis of acute, bilateral, nontraumatic motor impairment is showed in Fig. 11.1: basically, the absence of sensory deficiency suggests a muscular or neuromuscular pathology, or a mesial bifrontal lesion (which however should be associated with a frontal syndrome).

The differential diagnosis of acute, nontraumatic para-/tetraplegia is illustrated in Fig. 11.2, while the therapeutic approaches are described in Fig. 11.3.

Injury Level: Clinical Implications and Assessment Scales

Level Diagnosis in Spinal Cord Syndromes

“Level diagnosis” refers to the clinical process aiming to define the site of a spinal cord injury in the longitudinal direction and usually represents the first and one of the most important diagnostic questions. Useful elements for level diagnosis:

- Presence of segmental symptoms that may suggest the level of the lesion: paralysis and atrophy of specific muscle groups

Table 11.2 Differential diagnosis of nontraumatic, acute para-/tetraplegia

Vascular myelopathies
Ischemic <ul style="list-style-type: none"> • Primary (atherosclerosis, cardioembolism, vasculitis) • Secondary (vascular compressions by space-occupying lesions, aorta pathologies)
Hemorrhagic: epidural/subdural hematoma, subarachnoid hemorrhage, intraparenchymal (hematomyelia)
Vascular malformations: dural fistulas, angiomas, cavernomas
Inflammatory/infectious myelopathies
Without spinal cord compression <ul style="list-style-type: none"> • Acute transverse myelitis: viral (HSV, West Nile virus, <i>Enterovirus</i>, <i>Poliovirus</i>), bacterial (<i>Mycoplasma</i>, <i>Chlamydia</i>, tuberculosis, <i>Borrelia</i>), fungal, para- or postinfectious, or postvaccinal • Myelitis during inflammatory CNS disease (multiple sclerosis, optic neuromyelitis, ADEM, neuroborreliosis) • Myelitis during systemic inflammatory disorders (neuro-Behçet, Sjogren's syndrome, SLE, Wegener's granulomatosis, sarcoidosis)
With spinal cord compression <ul style="list-style-type: none"> • Epidural abscess • Peridural abscess • Spondylodiscitis
Noninflammatory expansive disorders
Spinal disc herniation, vertebral fracture
Primary or secondary neoplasms

(Table 11.3) and/or disappearance of specific deep tendon reflexes; level of hypo-anesthesia.

- Spasticity has a relative topographic diagnostic value: a spastic paraplegia indicates a spinal cord lesion below the cervical level, while spastic tetraplegia points to a high cervical lesion.

Assessment Scales

The magnitude of spinal cord damage is measured using the ASIA [2] scale (Table 11.4). In addition to the direct, event-related **primary damage**, there is a **secondary damage**, which occurs later (within

Figure 11.2 Differential diagnosis of myelitis. See also Chap. 6

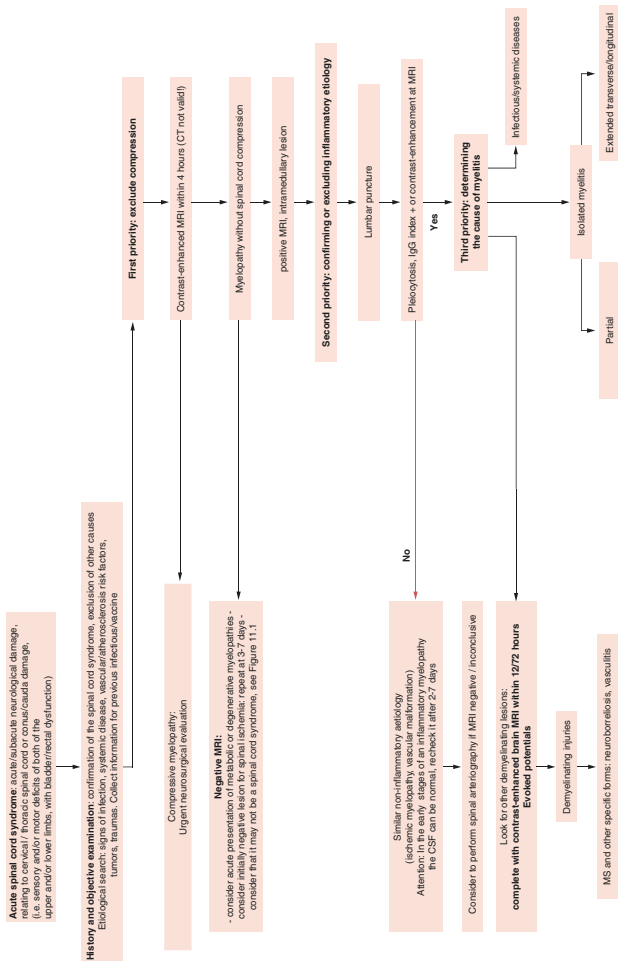


Figure 11.3 Therapeutic approaches

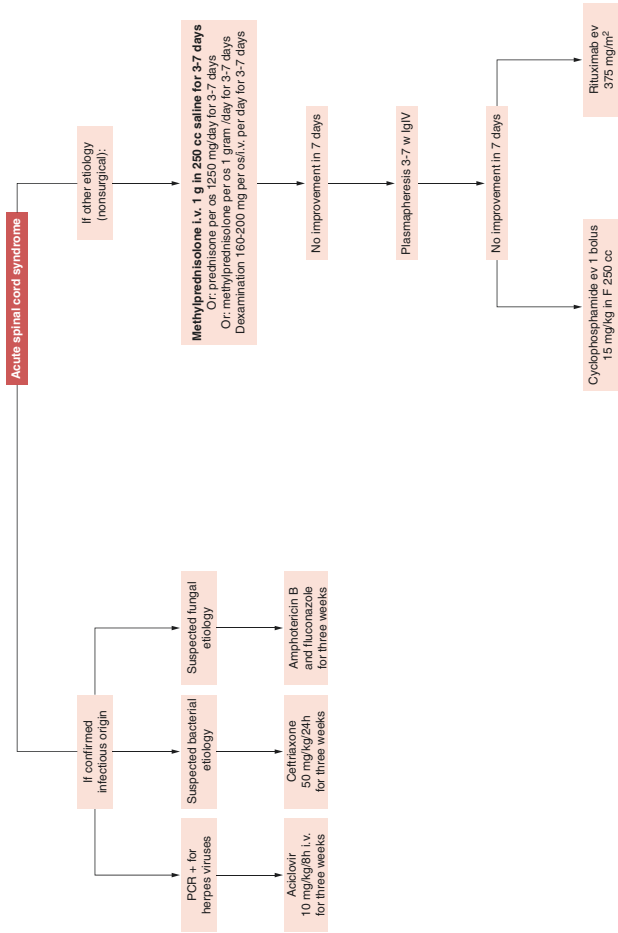


Table 11.3 Muscles to be tested to establish the motor lesional level [1]

Elbow flexors (C5)
Wrist extensors (C6)
Elbow extensors (C7)
Finger flexors (C8)
Abductor digiti minimi (T1)
Thigh flexors (L2)
Knee extensors (L3)
Dorsal flexors of the ankle (L4)
Extensor hallucis longus (L5)
Plantar flexors of the ankle (S1)

Keep in mind that in post-traumatic lesions (e.g., vertebral fractures), the skeletal and neurological levels may not coincide due to proximalization of the spinal cord during endouterine development. The neurological level corresponds to the fracture site only at the cervical level

the next few hours), related to hypoxic, inflammatory, ischemic mechanisms, to which may contribute both local (vasospasm, loss of self-regulation) and systemic factors (cardiovascular instability/hypotension in case of neurogenic shock, hypoxia from respiratory dysfunction). The 72-h ASIA score can therefore be more reliable for prognostic judgment than the acute phase evaluation [3].

Systemic Effects of Spinal Cord Injury

Cervical spinal cord damage, especially if post-traumatic, can be associated with neurogenic shock (19% of cervical lesions and 7% of thoracic lesions higher than T6).

Neurogenic shock is characterized by the presence of hypotension associated with bradycardia and peripheral vasodilatation, resulting in warm extremities. Hypotension is due to a loss of sympathetic tone and a reduction in peripheral vascular resistance, bradycardia to a prevalence of vagal tone in case of high cervical lesion that damages the sympathetic cardiac efferences.

Neurogenic shock should therefore be distinguished from hypovolemic shock (which may also be present or suspected in a post-traumatic context, for example, in case of major bleeding), which instead is characterized by hypotension with tachycardia and vasoconstriction, with cold extremities.

Spinal shock (a comprehensive term including all the physiological mechanisms triggered by spinal cord injury, almost always post-traumatic, leading to neurogenic shock) begins within minutes from the event and can last up to 6 weeks and more but is most evident in the first 2 weeks; it is characterized by areflexia and hypotonia, while its resolution is recognized by the recovery of tone and deep tendon reflexes.

Neurogenic shock is suspected if the systolic blood pressure is lower than 90 mmHg and the heart rate is lower than 80 bpm. The shock must be treated promptly, to avoid medullary hypoperfusion and secondary damage: *plasma expanders* (isotonic) up to 2 l are used if blood pressure <85 mmHg, for at least 1 week, monitoring diuresis (if lower than 30 ml/h, low-dose dopamine is usually added, 2–5 mcg/kg/min).

After the period of spinal shock, especially in case of lesions above T6, autonomic dysreflexia may occur, featured by unpredictable episodes of pressure rise, associated with sweating and bradycardia and alternating with episodes of orthostatic hypotension. It is thought to be a consequence of an abnormal autonomic response to sublesional stimuli: often, the positioning of the bladder catheter or an overdistension of the bladder and rectum can act as a trigger [4].

Respiratory Dysfunction

In the initial neurological assessment, it is important to try establishing the level of sensory/motor lesion, in order to target neuroimaging and assess the risk of respiratory dysfunction, especially if the patient has to be transferred by ambulance to another facility for care. Table 11.3 shows the muscle groups to be examined to determine the level of the spinal lesion. Also, clinical signs of

Table 11.4 ASIA scale [2, 3]

A. Complete	Complete motor and sensory deficiency at S4–S5 level
B. Incomplete Sensitive	Complete motor impairment with preservation of sensitivity below the neurological level including S4–S5
C. Incomplete motor	Voluntary motility is preserved below the neurological level, and more than half of the key muscles have a score lower than 3
D. Incomplete motor	Voluntary motility is preserved below the neurological level, and more than half of the key muscles have a score ≥ 3
E. Normal	No neurological impairment (normal muscle strength, intact sensitivity, normal sphincter functions, but possibly altered deep tendon reflexes)

Pay attention. To define a spinal cord lesion as incomplete from a motor point of view (C/D levels), there must be either voluntary anal contraction or partial sensory and motor savings of more than three metamers below the motor level

dysfunction of the inspiratory muscles should be explored (reduced thoracic expansion while inhaling, tachycardia, paradoxical movement of the thoracic wall, activation of accessory muscles). Injuries above T4 are associated with a high risk of respiratory failure, while for lesion below T4 respiratory function is gradually more likely to be preserved, up to T11 and below, where there is no actual risk of respiratory dysfunction and coughing is effective. More in detail:

- C1–C2 lesion: residual vital capacity (VC) 5–10% of normal, complete abolition of cough reflex.
- C3–C6 lesion: VC 20% of normal, coughing is possible but weak and ineffective.
- T2–T4 lesion: VC 30–50% of normal, coughing is present but weak.
- Spinal cord integration centers:
 - Diaphragm: C3–C5.

- ❑ Inspiratory muscles: internal intercostals (T1–T10), SCM (XI), scalenes (C3–C8).
- ❑ Expiratory muscles: abdominal muscles (external oblique, internal oblique, transverse, rectus abdominis), external intercostal muscles (T1–T11).

Perineal Dysfunction

The assessment of a possible perineal dysfunction (which has to be investigated on both the sensory and motor sides) has a prognostic significance: it defines the completeness of the lesion and the possibility of motor recovery; the assessment is more reliable after the period of spinal shock [5].

Micturition disturbances occur in 50–100% of spinal cord lesions of various nature (in rare cases, they occur at onset, before the development of sensory and motor signs), with different patterns depending on the site of the lesion (supra-sacral, sacral, post-sacral/cauda) and the main involvement of sensory or motor fibers.

In the spinal shock phase, the bladder is always areflexic and hypotonic (paralysis of the detrusor, unawareness of bladder filling): the clinical picture is that of acute urinary retention, eventually followed by incontinence due to extreme filling. The absence of the bulbocavernosus, pudendal-anal, and cremasteric reflexes confirm the neurological origin of bladder dysfunction in unclear cases (e.g., if other signs of spinal cord involvement are missing or in isolated partial lesions of the conus and the cauda, in which motor involvement may lack).

Clinical management in the emergency setting is limited to the positioning of a bladder catheter.

After a variable period (from a few days up to 12 weeks), the sublesional reflex activity reappears, and the sphincter disorders assume different and more peculiar characteristics, illustrated in Table 11.5, according to the site of the lesion [6].

Table 11.5 Neurogenic bladder: distinctive patterns depending on the site of the lesion

Detrusor (D) vs. external urethral sphincter (S)	Injury site	Clinical picture
D+, S+ (co-contraction during micturition: D–S dissinergy)	Above sacrum	Complete <ul style="list-style-type: none"> – Loss of voluntary inhibitory control of urination – Frequent urination with incomplete emptying; sometimes urge incontinence – Small bladder with reduced compliance, hyperreflexive Incomplete <ul style="list-style-type: none"> – Synergistic S relaxation can be preserved, and there may be complete emptying, but usually there remains urge incontinence
D–, S+	Conus medullaris	<ul style="list-style-type: none"> • Loss of parasympathetic control over D, acontractile • Urinary retention. Voluntary urination sometimes possible using abdominal muscles, but with incomplete emptying
D–, S–	Cauda S2–S4	<ul style="list-style-type: none"> • Loss of control on D (parasympathetic) and on S (somatic) with or without sensory deafferentation • Insensitivity to bladder filling: dilated bladder for increased compliance, acontractile • Absence of micturition reflex • Urinary retention with stress incontinence
D+, S– or normal	Above pons	<ul style="list-style-type: none"> • Loss of inhibitory control • Neurogenic D hyperactivity • Non-inhibited D contractions determine urinary frequency, urgency, and urge incontinence • Post-micturition bladder residue is absent or insignificant

Legend: + hyperactive/hyperreflexic, – flaccid or hyporeflexic. In the spinal shock phase, bladder is always hypotonic and areflexic. In the following weeks, the pattern of the urinary disorder varies depending on the site of the lesion. In the table are represented the four main mechanisms; however, in reality there are mixed aspects depending on the magnitude of the injury and the presence of comorbidities or compensatory mechanisms [6]

Causes of Acute Paraplegia and Tetraplegia

Vascular Myelopathy

Ischemic Myelopathy

Although more common than hemorrhagic myelopathies, ischemic myelopathies are much rarer than cerebral cerebrovascular disorders (accounting for 1% of all strokes and 5% of acute myelopathies). In fact, spinal arteries are rarely affected by atherosclerosis; also, the vascular suppliers of the spinal cord (three longitudinal arteries: the anterior spinal artery is a single vessel beading the anterior two-thirds of the spinal cord, and the two posterior spinal arteries, one per side, beading the posterior third of the spinal cord) have many extra- and intraspinal collateral arteries, connected to each other by complex anastomoses [7].

Potential causes of spinal ischemia include vasculitis, aortic surgery, embolism, aortic/vertebral dissection, prothrombotic states, but also severe hypotension and/or cardiac arrest. The clinical picture depends on the artery involved. Ischemic myelopathy may be suspected in the following cases:

- Hyperacute course: complete syndrome within a few minutes or hours.
- In case of involvement of the anterior spinal artery (which is actually the most frequent event):
 - “Belt” or radicular pain, *followed by*:
 - Flaccid para- or tetraplegia (more commonly paraplegia due to a thoracic lesion)
 - Bladder/rectal dysfunction
 - Loss of thermal sensitivity and pain below the level of the lesion, with preserved vibration and proprioception sensitivity (sensory dissociation)
 - MRI can show elongated lesions in the anterior spinal cord, but may be normal in the first 24 h
- In the very rare case of involvement of the posterior spinal artery, it is usually a bilateral and simultaneous impairment, with:

- Ataxia due to lesion to the posterior cord
- Paralysis (if the lateral motor fibers are affected as well)
- MRI can show a triangle-shaped lesion located in the posterior cord, but may be normal in the first 24 h

Spinal ischemias can be classified into:

- Primary: atherosclerosis, embolism, and vasculitis of spinal vessels during systemic vasculitis.
- Secondary: compression of spinal arteries by tumors/abscesses or other causes; it should be noted that these are also surgical emergencies as they can be treated with early decompression.

An underlying pathology of the aorta (dissection or complicated aneurysm) must be kept in mind: for exploring this opportunity, ultrasounds of the abdominal vessels and CT-angiography must be performed. In these cases, the spinal cord injury is usually located in the medium or lower thoracic segment; symptoms may be fluctuating.

Spinal Hemorrhage and Vascular Malformations

As for intracranial bleeding, spinal bleeding can be subarachnoid, intraparenchymal (hematomyelia), epidural, and subdural (these latter often representing surgical emergencies). The most frequent cause is trauma, possibly associated with a predisposing systemic condition (e.g., during anticoagulant therapy), but there are also spontaneous bleeding, usually in the context of cavernous angiomas (Rendu-Osler's disease), arteriovenous malformations, dural arteriovenous fistulas or spinal tumors. Epidural bleeding can also complicate simple procedures such as lumbar puncture.

The clinical presentation is practically indistinguishable from the ischemic forms (pain occurs typically at onset; however, motor deficit is more often incomplete, especially at the onset): MRI is required for differential diagnosis.

MRI findings vary according to the timing after onset. In the first 24 h, the hematoma usually appears isointense in T1-weighted sequences and hyperintense in T2-w; after 24 h it becomes hyperintense in T1-w and T2-w.

Vascular malformations (dural fistulas, more common in men after the fifth decade, or intramedullary arteriovenous malformations, more common in the second decade) can determine coexisting hemorrhagic (due to venous congestion) and ischemic mechanisms (due to “stealing” mechanisms).

The clinical picture is characterized by progressive paraplegia with periodic, acute, or subacute deterioration, sometimes transient, which typically occurs while standing or walking.

The diagnosis requires MRI (extended longitudinal hyperintense lesion in T2 and/or serpiginous *enhancement* in T1-w, tortuosity of the vessels on the spinal cord surface) and possibly MRI-angiography; angiography is required to complete the diagnostic evaluation and to set the correct treatment.

Inflammatory and/or Infectious Myelopathies

Acute inflammatory disorders can affect the spinal cord by producing myelopathy directly (myelitis) or secondary to compression: also in these cases MRI is crucial.

Isolated, idiopathic myelitis should be distinguished from myelitis occurring in the context of a systemic or CNS-restricted inflammatory disease (multiple sclerosis or optic neuromyelitis) or due to a direct infection [8] (Fig. 11.2).

A history of previous infectious or vaccination is suggestive for postinfectious transverse myelitis, i.e., caused by an immune reaction triggered by the infectious event; however, the absence of a symptomatic previous event does not rule out this diagnosis. The clinical onset during an infectious event suggests a direct, more often viral, infection. Any signs and symptoms of systemic inflammation should also be investigated [9].

Only after having excluded any extrinsic compressions by performing MRI, the examination of the CSF is always indicated, both to confirm the diagnosis and for the differential diagnosis with inflammatory diseases of the CNS (presence of oligoclonal bands);

to explore this hypothesis, the execution of multimodal evoked potentials is also useful [10].

The most frequent causes of extrinsic compression, among inflammatory etiologies, are spondylodiscitis and epidural abscesses, usually caused by bacterial infection (more often staphylococci, more rarely streptococci, Gram-negative bacteria, and rarely mycobacteria). A typical predisposing condition causing immunodepression has to be investigated (diabetes, congenital or acquired immunodepression, chronic disabling diseases). According to clinical history, in select cases the iatrogenic causes must be taken into account (e.g., after epidural injections).

Spondylodiscites often involve the thoracic or lumbar spine. Symptoms are often nonspecific or may even be clinically silent and only manifest when neurological symptoms develop from the involvement of spinal cord and/or nerve roots.

Here, too, the crucial test for making the correct diagnosis is the MRI.

The clinical course of the epidural abscesses, usually located at the thoracic level, is initially featured by local pain, with or without radicular involvement; signs and symptoms of systemic infection may be variably complained. With disease progression, a paraplegia develops with sensory level and bladder and rectal dysfunction.

The key elements triggering the clinical suspicion can be summarized as follows: a relatively slow course, the presence of infectious foci in other sites, and the pain. Also in these cases, the major diagnostic exam is the MRI. Treatment includes surgical approach and long-term antibiotic therapy. Prognosis is influenced by the promptness of diagnosis and the extent of motor damage at the time of diagnosis.

Noninflammatory Expansive Diseases

The damaging mechanism is that of compression of the spinal cord, which can occur directly or indirectly, through occlusion of the vessels. Compression is the most common cause of myelopathy in the elderly, usually determining a chronic myelopathy, but there may be an acute or subacute presentation in the case of rapidly growing tumors (e.g., metastases) or pathological vertebral fractures, or in the case of intratumoral bleeding/ischemia. In addition, the possibility of an intramedullary localization of lymphoma should also be kept in mind, a possibility that can be difficult to detect because of its notable steroid-sensitivity, both clinically and radiologically. It has to be suspected especially in case of recurrence in the same location or persistence of contrast-enhancement at imaging.

Sometimes spinal cord damage can complicate radio and/or intrathecal chemotherapy (particularly methotrexate or cytarabine). Usually these toxicity myelopathies have a subacute-chronic onset, but occasionally they can present acutely-subacutely in the context of a paraneoplastic syndrome such as motor neuron syndrome (subacute onset, with progressive and asymmetrical course, often associated with lymphomas and anti-Hu antibodies+), necrotizing myelopathy (a rapidly ascending acute medullary syndrome, more often associated with non-Hodgkin's lymphomas and anti-ANNA3 antibodies), or subacute sensory neuronopathy (loss of proprioceptive and vibratory sensitivity rather than superficial, resulting in sensory ataxia; more often associated with pulmonary microcytomas and anti-Hu antibodies+) [11].

Among benign causes, disc herniation has to be mentioned. Often located at the level of L3–L4 or L4–L5 (less frequently, thoracic or cervical) is able to compress the cauda leading to a flaccid paralysis, sensory deficit, and sphincter dysfunction.

Para- and Tetraplegia in Intensive Care Unit

Figure 11.1 describes the differential diagnosis of bilateral acute motor impairment. For some of the listed pathologies, the term para-/tetraplegia is used as a facilitator. However, the clinical picture of extreme motor deficit is inaccurate in topographical terms because the site of the damage can vary from the CNS to the peripheral nerves.

The forms of para-/tetraplegia that the neurologist most often encounters in the Intensive Care Unit (ICU) involve either the peripheral nerve or muscle, or both.

The Intensive Care Unit Acquired Weakness (ICUAW) is an acronym for a relatively recent definition [12], which describes a clinical syndrome that includes several pathophysiological entities: the Critical Illness Polyneuropathy (CIP), the Critical Illness Myopathy (CIM), or their concomitance, in the form of Critical Illness Neuro-Myopathy (CINM) (Consensus Meeting in 2009) (Table 11.6).

It is difficult to estimate the exact incidence of the ICUAW, in the absence of systematic studies; however, it is thought to be relatively common, affecting 30–60% of patients who remain in Intensive Care Units for more than 7 days [13]. Also, the prevalence is increasing due to the improved survival of such patients.

Table 11.6 The distinguishing features between CIP and CIM

Site involvement	CIP	CIM
Motor impairment distribution	>Distal	>Proximal
Facial muscles External ocular muscles	Normal	Often involving facial muscles, rarely extraocular muscles
Sensory	Altered, >distal	Normal
Deep tendon reflexes	Reduced or absent	Normal or reduced
Respiratory muscles	Frequent	Frequent
Neurovegetative dysfunction	Possible	Absent

The main risk factors are sepsis (possibly complicated by multiorgan failure, MOF), SIRS (systemic inflammatory response syndrome during sepsis, trauma, or burns, characterized by fever, tachycardia, tachypnea, leukocytosis), prolonged immobilization, steroid treatment for more than 10 days, invasive ventilation for more than 7 days, hyperglycemia, and use of neuromuscular blockers for more than 3–5 days.

Other, less relevant, risk factors are represented by older age, female gender, hypoalbuminemia, malnutrition, the need to use vasopressor drugs, and aminoglycosides.

Obviously, the ICUAW may also be present in departments other than the Intensive Care Unit if similar conditions occur.

The pathogenesis is thought to be multifactorial, including a dysfunction of the microcirculation, oxidative stress associated with systemic inflammation, inactivation of the sodium channels, a dysfunction of the mitochondria and the production of ATP, and direct muscle damage mediated by proteases.

Clinically, the following features are observed:

- Flaccid para-/tetraplegia, preserving facial muscles
- Respiratory failure/difficult weaning from the mechanic ventilator but with normal gas exchange (due to muscular failure, which clinically involves the diaphragm to a greater extent than the accessory respiratory muscles)

Factors that can delay the diagnosis, typical in ICU patients, are the presence of subcutaneous edema (potentially masking muscular atrophy), the administration of sedative drugs or neuromuscular plaque blockers (preventing a complete neurological evaluation), and the incorrect attribution of respiratory failure to cardiac or pulmonary causes.

Furthermore, some borderline situations have to be mentioned:

- Coexisting Guillain-Barré syndrome and ICUAW:
 - *Scenario 1:* Patient with GBS, hospitalized in ICU, who after a few days gets worse: exacerbation of Guillain-Barré syndrome or CIP?

- *Scenario 2:* Patient with severe sepsis, admitted to ICU, develops muscle weakness after a few days: Guillain-Barré syndrome or CIP?

In these cases, the differential diagnosis can be allowed by CSF examination (which is expected to be normal in the CIP) and the EMG (in case of demyelinating neuropathy the first hypothesis is a Guillain-Barré syndrome).

- Diaphragm paralysis may be linked to the ICUAW but may also be induced by orotracheal intubation (ventilator-induced diaphragmatic dysfunction, VIDD), strictly dependent on the duration of intubation.
- Diseases with rapid course, unknown before hospitalization in the ICU, acutely presenting with para-/tetraplegia or respiratory failure at acute onset (ALS, myasthenia gravis, myopathy).
- Coexisting brain damage, for example, due to septic encephalopathy or focal brain lesions, which can alter the evaluation of muscle strength.

The distinction between CIP and CIM (Table 11.6) can be difficult, as muscle damage can also occur as a consequence of nerve damage. The diagnostic criteria for the diagnosis of ICUAW are as follows:

- Muscle weakness that occurs a few days after a critical illness: generalized, flaccid, symmetrical muscular
- Generalized muscular weakness, flaccid, symmetrical, usually sparing the cranial nerves (facial grimaces are preserved)
- Average score at the MRC scale of less than 48 in the testable muscles
- Dependence on mechanical ventilation
- Exclusion of other causes of para-/tetraplegia

The evaluation of muscle strength obviously requires the collaboration of the patient, and in an ICU department, this is not always possible, and in any case does not allow to easily discriminate the cause of the motor impairment.

From this perspective, electromyography is fundamental, enabling to distinguish myopathy from a peripheral nerve or neuromuscular plaque disease and to distinguish between axonal or demyelinating

involvement as well. This is important also for estimating prognosis, which should be better in patients with CIM and worse in patients with CIP.

Complementary investigations include also lab tests for determining blood levels of CPK, hemogasanalysis values, and ultrasounds to evaluate the mobility of the diaphragm.

The therapeutic approach of the ICUAW consists essentially in the control of predisposing factors and conditions: aggressive treatment of sepsis, treatment of hyperglycemia, limitation of steroid use, neuromuscular and sedative blockers, early mobilization of the patient, and parenteral nutrition to prevent catabolism.

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12.

Head Injuries

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Definition and Epidemiology

A cranio-encephalic trauma (TBI) is defined as a traumatically induced structural insult and/or an alteration of physiological brain functions as a result of an external force that produces the onset or worsening of at least one of the following clinical symptoms:

- A period of altered level of consciousness
- Any loss of memory of events that occurred immediately before or after the trauma

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- An impairment of the psychic state at the time of trauma (confusion, disorientation, psychic slowdown)
- The presence of transient or persistent focal neurological deficits

Head trauma may not be associated with immediate clinical symptoms but may develop only afterwards. A skin and/or bone lesion is found to confirm head trauma, but the detection of computer tomography (CT) free of lesions does not exclude the presence of brain damage. In fact, in the absence of neuroradiologically evident lesions, there may be a **concussion** of the brain, a term that defines a cascade of metabolic events associated with neuronal dysfunction induced by the traumatic event.

The head trauma can be defined as *closed* or *open*; the latter is associated with damage to the dura mater, which leads to the presence of pneumocephalus (intracranial air) and/or loss of liquor.

Head trauma can result in both *primary* brain damage (direct damage from traumatic impact) and *secondary* damage (as a result of a cascade of processes that are activated after the trauma).

Head trauma is a common cause of access to emergency rooms, especially in developed countries, with 262/100,000 cases per year in Europe [1] and about 1.7 million people per year in the United States [2]. In Italy, the incidence in age classes older than 70 years (30/100,000) is almost double that of the age class normally assumed to be most at risk (18–24 age range, rate of 18/100,000), while in Europe [3, 4] and the United States [5] the incidence in the 15–24 years age group (32.8/100,000) is slightly higher than in the older than 65 years age group (31.4/100,000). Although injuries attributable to road accidents fell from 39% in 2003 to 24% in 2012, those attributable to falls increased from 43% to 54% respectively, with an increase in elderly traumatized persons (>65 years) [6].

The World Health Organization estimates that TBI is the leading global cause of death and disability among all trauma-related diseases. Although there are no recent estimates, it has been

calculated that in Italy about 250 patients per 100,000 inhabitants are admitted in hospital with a mortality rate of 17 cases per 100,000 inhabitants per year, equal to 6.8% of all cases [7].

Diagnosis and Evaluation Scales

The diagnostic framework of the consequences of a head injury is primarily based on a competent clinical evaluation that allows determining:

- The severity of the clinical picture
- The dynamics of the event
- The prognostic factors of clinical deterioration
- The implementation of a suitable diagnostic-therapeutic path

The clinical evaluation is based on the general objective examination, which includes a careful inspection of the skull and face, and on the neurological examination, aimed at highlighting the level and content of consciousness and any focal deficits resulting from the damage of the nervous system.

The universally accepted instrument for the staging of post-traumatic clinical symptoms (Table 12.1) is the Glasgow Coma Scale (GCS) [8, 9]. This scale stratifies the head trauma into three degrees of severity: mild, moderate, and severe (Table 12.2). Severity should not be wrongly related to the modality and dynamics of the trauma but just to the degree of alteration of the patient's state of consciousness (Table 12.3), despite the traumatic event. Therefore, after a mild traumatic event such as a fall to the ground for a stumpler, a severe head trauma could be observed. At the same time, after a road traffic accident the car driver can report a mild head injury. On these assumptions, a classification was created to define the extent of the traumatic event (Table 12.3).

Based on the result of GCS, and other anamnestic data about loss of consciousness (LOC), post-traumatic amnesia (PTA) and specific risk factors potentially influencing TBI evolution and outcome (RF), trauma is divided into syndromic pictures described in Tables 12.2, 12.3, 12.4, 12.5, 12.6, and 12.7 according to the guidelines of the European Federation of Neurological Societies (EFNS) [10, 11].

Table 12.1 Glasgow Coma Scale/score

Function	Score		
Eye opening response	None	1	Not responder to any stimuli
	To pain	2	Opening to fingertip painful stimuli (such as pinching the skin or pressure on the sternum, supraorbital rim)
	To verbal command	3	Eyes open to verbal command, speech or shout
	Spontaneous	4	Eyes open spontaneously, not necessarily conscious
	Not testable	NT	If local injury, oedema, or otherwise not allow to assess
Verbal response	None	1	No verbalisation of any kind
	Incomprehensible	2	Grunts/gemites, no language
	Inappropriate words	3	Intelligible, not prolonged sentences
	Confused	4	Confused, but able to answer questions coherently
	Oriented	5	Aware of time, place and name
	Not testable	NT	If local injury, oedema, or otherwise not allow the communication. VT means intubated patient
Motor response	None	1	Whatever the pain, the limb stays flabby
	In extension	2	Accentuated by painful stimuli: internal rotation of the shoulder, pronated forearm, extended elbow, flexion of the wrist, leg extension and plantar flexion (decerebrate posturing)
	Abnormal	3	Accentuated by painful stimuli: internal rotation of the shoulder, flexion of forearm, wrist, leg extension and plantar flexion (decorticate posturing)
	Withdrawal from pain	4	Far away from the pain of the limb, the shoulders are abducted
	Localize the painful stimulus	5	Limb attempts to ward off painful stimulus (over-orbital/thoracic pressure)
	Obeys commands	6	Obeys simple commands
	Not testable	NT	If local injury, oedema, or otherwise not allow the movements

Score: sum of the points of the three components (varies from 3/15 to 15/15)

Table 12.2 National and international classification of head injury based on GCS score

International classification		ASSR trauma 2006	
Mild	13–15	Light	14–15
Moderate	9–12	Moderate	9–13
Severe	≤8	Severe	≤8

Table 12.3 Development of brain damage in different types of head trauma

Light	GCS = 13–15
Category 0	GCS = 15 No LOC, no PTA, no TBI. No-risk factors
Category 1	GCS = 15 LOC <30 min, PTA >1 h No risk factors
Category 2	GCS = 15 Presence of risk factors
Category 3	GCS = 13–14 LOC <30 min, PTA >1 h With/without risk factors
Moderate	GCS = 9–12
Severe	GCS ≤ 8
Critical	GCS = 3–4, absence of pupillary reactivity and absence of motor response or response in decerebration

The development of brain damage is more likely following moderate or severe trauma

More than 95% of head injuries are classified as mild; within this category, individuals with a low or high risk of developing brain damage can be identified on the basis of the presence or absence of clinical features or risk factors (Table 12.4)

TBI traumatic brain injury, *GCS* Glasgow Coma Scale, *LOC* loss of consciousness, *PTA* post-traumatic amnesia

The evaluation of GCS should be carried out and communicated as the resulting value of the three items, as well as the value of the sum, for example, GCS 13/15: Verbal response (V) 4, Eye opening (O) 4, and Motor response (M) 5.

Table 12.4 Mild head injury or concussion

	GCS 13–15	LOC +/-	PTA +/-	
<i>Within the mild trauma, the EFNS [9, 10] identified four levels:</i>				
Grade 0	GCS 15/15	LOC –	PTA –	RF –
In the absence of neurological signs, it is inappropriate to speak of <i>brain</i> trauma since it is <i>head</i> trauma.				
Grade 1	GCS 15/15	LOC <30 min	PTA <1 h	RF –
In this case, it is a trauma of the brain and therefore are recommended but not made mandatory neuroradiological investigations such as cranial CT or at least Rx.				
Grade 2	GCS 15/15	Irrelevant LOC	PTA irrelevant	RF +
The presence of risk factors (RF), regardless of the clinical picture, should lead to a cranial CT scan. The risk factors are listed in Table 12.5.				
Grade 3	GCS 13–14/15	LOC irrelevant	PTA irrelevant	RF irrelevant
A GCS grade of less than 15/15 makes it mandatory to perform a cranial CT scan, regardless of whether or not other deficits such as loss of consciousness and amnesia are present.				

Table 12.5 Risk factors for the development of brain damage as a result of mild head injury

- Unclear or ambiguous history of trauma
- Persistent post-traumatic amnesia (could be interpreted as verbal response to GCS = 4 and then GCS < 15)
- Retrograde amnesia >30 min
- Trauma over the clavicle including clinical signs of cranial fracture (basic cranial fracture or fracture with depression of the theca)
- Severe, diffuse, persistent headache
- Repeated vomiting
- Focal neurological deficits
- Epileptic seizures
- Age <2 years
- Age >60 years
- Coagulopathy
- High-energy trauma dynamics or polytrauma
- Alcohol/drug abuse

Table 12.6 Criteria for identifying “high-energy trauma” proposed by Advanced Trauma Life Support (ATLS)

-
- Ejection from the car
 - Deceased in the same vehicle
 - Projected or rolled pawn
 - High-speed car accidents:
 - Initial speed >64 km/h
 - Vehicle deformation >50 cm
 - Intrusion into passenger compartment >30 cm
 - Extrication time >20 min
 - Falls from >6 m
 - Vehicle rollover
 - Cars against pedestrians at speeds >8 km/h
 - Motorcycle accident at speeds >32 km/h or with separation of rider from vehicle
-

Table 12.7 Upon arrival at the hospital

Upon arrival at the hospital is always advisable:

- Contact trained/specialised personnel (neuroscience unit)
 - Detect immediately if mild-moderate-severe or polytrauma
 - Exclude intoxication (alcohol, substances of abuse)
 - If polytrauma, perform ABCD and add specific diagnostic examinations (cervical CT, RX for possible fractures, etc.)
 - If GCS ≤ 8 contact anaesthesiologist
 - If TBI is mild, identify those with low or high risk of evolution
-

In some patients (with dementia or previous neurological deficits affecting motility, speech or cranial nerves), baseline pre-trauma GCS may be less than 15. In this case, this information must be reported.

Mild head trauma will be addressed separately from moderate and severe head injury due to different diagnostic and therapeutic assumptions for management.

The risk factors that make a mild head trauma worthy of greater consideration, in terms of risk of progression and neurological worsening, at the same level of moderate/severe trauma, are reported in Table 12.5. Table 12.6 shows the criteria for considering the event that caused the trauma as “high energy”, regardless of the patient’s clinic.

In the presence of these modalities, even in the absence of a clinic that lays down for medium to severe trauma, the patient should be considered at risk. In terms of aggravating factors for mild head trauma, the illustrations in Figs. 12.1 and 12.2 should be taken into account.

The diagnosis of possible traumatic brain injury should be considered:

- When a history of craniofacial trauma is reported
- When there are obvious signs of trauma on the skin of the skull or face
- In the elderly or in the patient at risk for coagulopathies, when there has been a trauma that did not directly involve the skull but may have produced a lesion of brain tissue or a subarachnoid or subdural haemorrhagic effusion

In mild head trauma, in the absence of significant extracranial lesions, the detection of serum levels of S-100 β <0.1 $\mu\text{g/L}$, within 6 h of the event could serve to differentiate the low-risk patient, who can be discharged without CT control from the moderate-risk patient [12, 13].

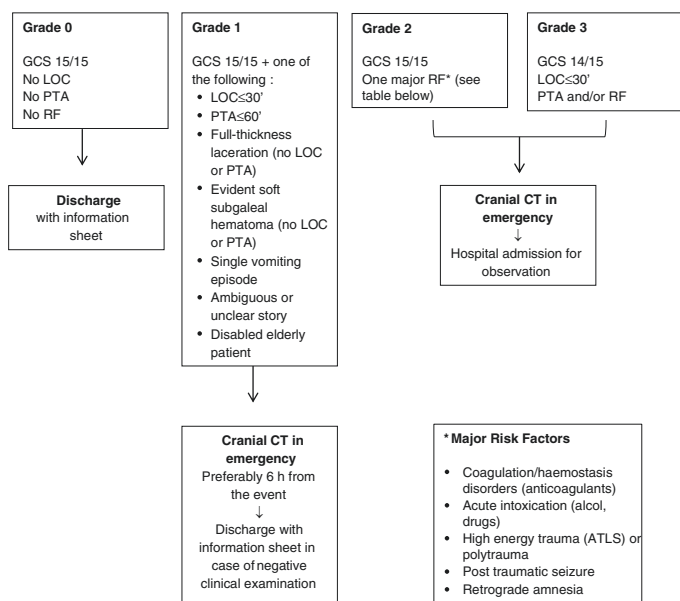
Mild head trauma does not require any specific medical treatment in the acute phase.

Moderate to Severe Head Injury

Moderate, severe, and critical traumas (GCS < 14 , Table 12.2) require intensive hospital care in dedicated facilities and must **always be hospitalized** (Table 12.8). They are staged according to the algorithm shown in Tables 12.9, 12.10, 12.11, and 12.12.

Following Emergency Department (ED) admission, for all cases when a cranial and/or spinal CT scan is indicated, a prompt transfer protocol to another hospital with neuroradiological facilities is mandatory in case of unavailable neuroradiological workout. It is advisable to transfer to a facility where neurosurgical counselling in ED (on site or by telemedicine) is available in addition to the CT

Figure 12.1 Decision-making algorithm for patients with mild head trauma



Patients with LOC >30' or PTA >60' fall into the category "moderate" head injury

GCS: Glasgow Coma Scale
LOC: Loss of Consciousness
PTA: Post Traumatic Amnesia
RF: Risk Factors
CT: Computerized Tomography

scan when indicated in terms of patient's clinical conditions and transfer's logistic.

Magnetic resonance imaging (MRI) is indicated in the presence of signs and symptoms related to spinal cord damage and in cases of suspected vascular damage (e.g. vertebral misalignment, fracture involving the transverse foramen or lateral processes or

Figure 12.2 Algorithm for the diagnosis and treatment of mild adult head injury

Algorithm for the diagnosis and treatment
of mild head injury in adults

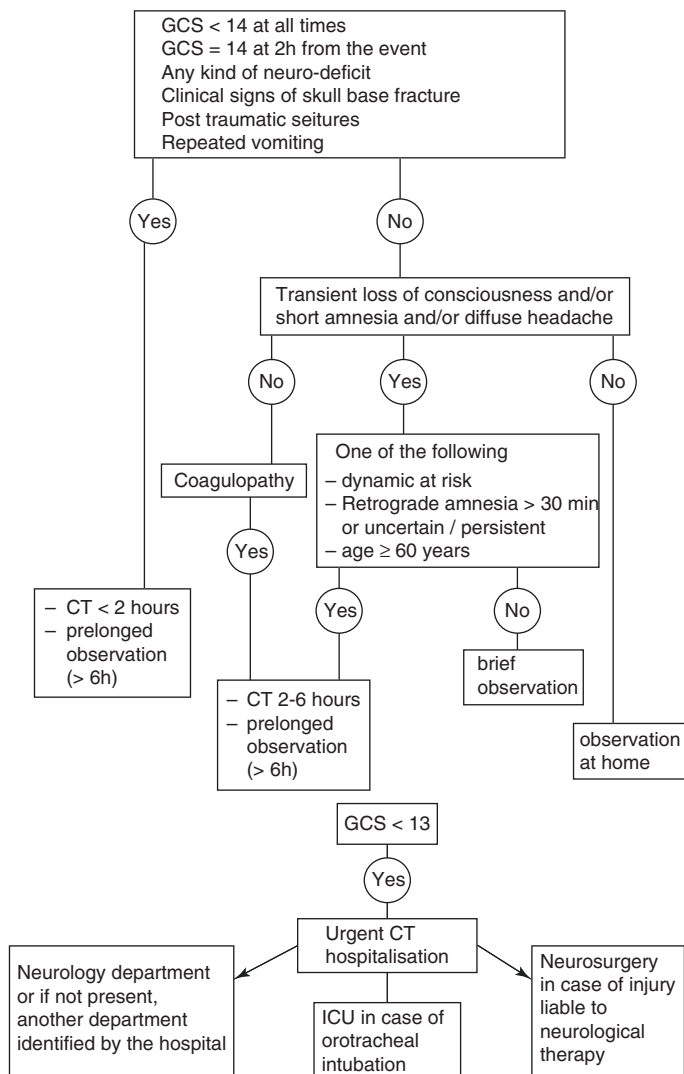


Table 12.8 The health emergency in terms of head trauma: criteria for hospitalisation

-
- Altered level of consciousness (GCS < 15)
 - Use of anticoagulants or other significant medical problems
 - GCS 15 but one of the following:
 - Persistent amnesia (>5 min)
 - Persistent nausea and/or vomiting
 - A post-traumatic seizure
 - Focal neurological signs
 - Irritability or behavioural changes
 - Clinical or radiological evidence of a cranial fracture or suspected penetrating wound
 - Skull CT alteration
 - Severe headache or other neurological symptoms
 - Patient with social problems or who cannot be observed by a reliable adult
-

Table 12.9 Indications for admission to the hospital without a specific department of destination

-
- Altered level of consciousness (GCS < 15)
 - Use of anticoagulants or other significant medical problems
 - GCS 15 but one of the following:
 - Persistent amnesia (>30 min)
 - Persistent nausea and/or vomiting
 - Post-event seizures
 - Focal neurological signs
 - Irritability or behavioural changes
 - Clinical or radiological evidence of a cranial fracture or suspected penetrating wound
 - Cranial CT scan abnormalities
 - Severe headache or other neurological symptoms
 - Patient with social problems or without the protection of a reliable adult
-

insufficiency of the vertebro-basilar circulation) and is mainly suggested by a previous CT scan and/or by neurological alterations. The timing of execution should be discussed in relation to the clinical case following local protocol.

Table 12.13 shows the classification of radiological pictures in cranial CT in TBI, according to the types of presentation [15–17].

Table 12.10 Guidance on the timing of cerebral CT scans in the case of TBI

To be performed immediately (urgency) if (one of the following)	To be performed within 6–8 h if GCS 15 with (one of the following)
<ul style="list-style-type: none"> • GCS ≤ 12 (eye opening to pain, does not speak) • GCS $> 12 < 15$ within 2 h from the event • Focal neurological deficit • Clinical suspicion of cranial fracture • Prolonged loss of consciousness (>5 min) • Post-traumatic epileptic seizures • Repeated vomiting (≥ 2 episodes) • Severe persistent headache • Known coagulation disorder 	Loss of consciousness or amnesia and: <ul style="list-style-type: none"> – Age ≥ 65 years – Disorders of coagulation – Risk of high energy trauma – Retrograde amnesia >30 min – Use of anticoagulants

Consider performing brain CT in patients who return to ED <48 h after the first access complaining of any disorder that may relate to the trauma. The execution of CT should be considered in all patients on anticoagulant therapy, even in the absence of loss of consciousness or amnesia [14]

Table 12.11 Recommended examinations associated with craniocerebral CT scan

Imaging of the cervical spine in cranial trauma	
RX in three projections of the cervical spine if: <ul style="list-style-type: none"> – Neck pain – Age >65 y.o. – Dynamic at risk It is considered dangerous to evaluate the excursion of the movements of the neck	Cervical spine CT (within 1 h) if: <ul style="list-style-type: none"> • GCS < 13 at initial assessment • Intubated patient • Suspected damage despite normal Rx if a certain diagnosis is required in urgency (e.g. for surgery) • Polytrauma

Table 12.12 Indications for transfer for cranial/spine CT execution and/or neurosurgical evaluation

<ul style="list-style-type: none"> • From hospital without CT if the patient falls within the cases of Tables 12.10 and 12.11 to hospital with CT and Neurosurgeon • From hospital without Neurosurgeon if cranial CT documents intracranial injury (Table 12.13) to hospital with Neurosurgeon • Independently of the results of cranial CT if clinical features suggest appropriate evaluation, monitoring and treatment by Neuroscience Units including neurosurgical competence
--

Table 12.13 Classifications of CT pictures in head trauma [15]

Interpretation of neuroimages	
Widespread, invisible damage	Intracranial damage not visible to CT
Diffuse damage	Visible cisterns with midline shift <5 mm, presence of lesions, but not hyperdense or mixed density lesions >25 ml
	May include bone fragments and foreign bodies
Diffused damage with oedema	Compressed or absent cisterns, shift <5 mm, no hyperdense or mixed density lesions >25 ml
Diffuse damage with shift	Midline shift >5 mm, no hyperdense or mixed density lesions >25 ml
Injuries with mass effect	Hyperdense or mixed density lesions >25 ml
Subarachnoid haemorrhage	Present or not

The diagnostic estimation is followed by the decisional algorithm for the department of hospitalization of the patient with moderate head trauma. The Department of Neurosurgery and the Department of Neuroscience, in a hospital with a Neurosurgery Unit, are the departments of choice for the patients listed in Table 12.14.

The neurosurgeon's assessment must be carried out in the first instance. Within the territorial emergency network, in the peripheral hospital with H24 radiological activity connected to the Trauma Centre equipped with H24 neurosurgeon, the evaluation can take place through telemedicine. The indications for hospitalization will, therefore, be arranged by local protocols that may vary in relation to the logistics of the various territorial networks. In the absence of a territorial network and a telemedicine system, the criteria for hospitalization in a hospital equipped with neurosurgery are broader (Table 12.14), due to the impossibility of remotely monitoring patients and their potential evolution.

Table 12.14 Indications for admission to hospital with a Neurosurgery Unit in the absence of a territorial system coordinated with telemedicine

-
- Intracranial lesion potentially susceptible to neurosurgical treatment
 - Prolonged coma ($GCS \leq 8$) after initial resuscitation
 - Persistent confusion >4 h
 - Deterioration of the level of consciousness (loss of 1 point in the motor or verbal items or 2 points in the eye-opening items of the GCS)
 - Neurological focal signs
 - Epileptic seizures without complete recovery
 - Cranial fracture (*compound depressed*)
 - Penetrating lesion ascertained or suspected
 - Loss of CSF or other signs of skull base fracture
-

Table 12.15 Clinical observation

The parameters to be observed are

- GCS
 - Pupils (size and reactivity)
 - Movements of the limbs
 - Vital parameters
 - PA
 - Saturation O_2
 - Heart and respiratory rate
 - Body temperature
 - Signs of behavioural or word alteration
-

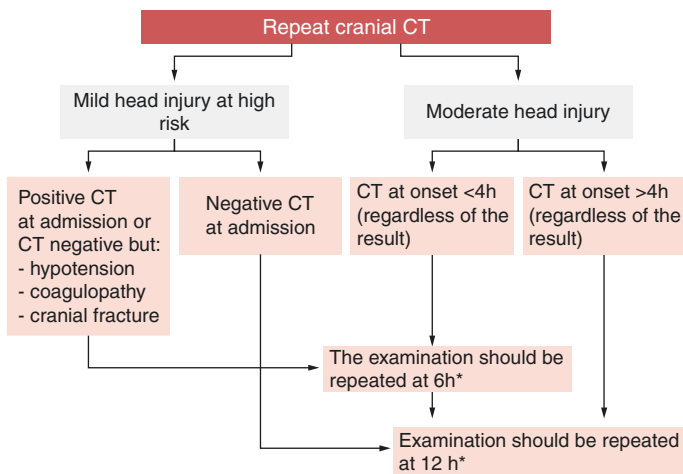
Frequency of observations

- Every $\frac{1}{2}$ h for 2 h
 - Every 1 h for 4 h
 - Every 2 h for 6 h
 - Following every 4 h until deemed no longer necessary
-

There are no studies to establish the timing

The following table shows the controls to be carried out in patients with moderate head trauma according to the evolution of the clinical picture (Table 12.15 and Fig. 12.3).

If the first CT scan is performed ≥ 4 h following trauma, a second 12-h CT scan can be considered if the neurological and clinical conditions are stable.

Figure 12.3 **Timing of radiological checks**

*In the absence of changes in clinical conditions leading to an earlier re-evaluation

Management of Severe Head Trauma

Head trauma is defined as severe for GCS ≤ 8 after immediate resuscitation procedures have been performed. However, the assessment of severity must take into account the presence of other variables (e.g. substance poisoning, sedation, intubation, etc.) that may affect the state of vigilance. Medical management of severe head trauma begins in the pre-hospital phase in order to prevent secondary damage [18–20] (Table 12.16).

The patient must always be admitted to the appropriate department equipped with h24/Intensive Care Neurosurgery in relation to the stability of vital parameters and the need for ventilatory support (Tables 12.17 and 12.18).

The monitoring of intracranial pressure is still under debate in terms of timing, indication, and outcome prediction, but shared and multidisciplinary management between neurosurgeons and neurointensivists is desirable.

Table 12.16 Pre-hospital management**Oxygenation**

- Continuous monitoring of O_2 and CO_2 at the end of exhalation
- Saturation maintenance $O_2 >90\%$
 - Supplement of O_2
 - Intubation if GCS < 9, inability to maintain airway, hypoxemia not correctable with O_2 therapy
- Control of normal respiratory acts (CO_2 at the end of exhalation 35–40 mmHg)

Blood pressure

- Maintain cerebral perfusion pressure (CPP) >90 mmHg with isotonic fluid therapy

Objective examination

- GCS
- Pupillary diameter assessment
- Signs of herniation

Transport at Trauma Centre

- Availability of 24 h CT scan, neurosurgical facilities and possibilities for monitoring and management of ICP (intracranial pressure)

Table 12.17 Management in the Department of Neuroscience**ATLS**

Airway assistance (avoid $SpO_2 <90\%$)

Cardiovascular support (avoid SBP <90 mmHg)

GCS and neurological examination

Anamnestic news, circumstances of the incident and place of exhibition

Systemic evaluation of trauma**ICP control**

Maintain the trunk at 30°

Keep the head in a neutral position (avoid hyperflexion and hyperextension)

Sedation and pain management

Eucharbia

Laboratory tests

Haemochrome with formula, complete chemistry

Coagulation tests

Toxicological tests

Alcohol

Pregnancy tests

Table 12.17 Continued**Radiology**

CT skull and spine in toto

CT total body in polytrauma

Evidence of herniation or neurological deterioration

Administration of osmotic therapy in bolus iv (mannitol with osmolarity <320 mOsm or hypertonic solution)

Eunatremia, euglycemia, normothermia**Anti-comitial prophylaxis (levetiracetam or phenytoin) in case of early seizures****Neurosurgical evaluation****Intracranial Pressure (ICP) Management**

- ICP treatment should be considered for values >20–25 mmHg, related to the time of maintenance of the values.
- CPP treatment should maintain a range of >60 < 70 mmHg.
- PRx (pressure reactivity index): <0.3.
- No contraindication for osmotic agents:
 - Hypertonic solution for chronically hyponatraemic patients.
 - Mannitol (avoid hypotension).
- Steroids are not recommended for improving outcome or reducing ICP.
- Barbiturate Coma and Decompressive Craniectomy should be indicated by a multidisciplinary neurosurgical and neuro-intensivist evaluation, based on clinical, neurophysiological, and neuroradiological findings and response to previous pharmacological therapies.

Pharmacological and Non-pharmacological Treatments

- *Endocrine hypertension:*
 - Mannitol (20%) 0.25–1 g/kg, boluses in 15–20 min; osmolarity <320 mOsm
 - Hypertonic solution (3%) 3–5 cc/kg; NaCl 7.5% + dextrose (efficacy not yet validated)
- *Nutrition:* basic calories intake at least by day 5–7

Table 12.18 Management of head trauma in the presence of changes in coagulation (modified by Frontera et al. [20])

First: suspend any antiplatelet/anti-coagulant therapy if it is not absolutely contraindicated

Antithrombotic	Antidote
Vitamin K antagonists	<p>If INR > 1.4:</p> <ul style="list-style-type: none"> • Vitamin K 10 mg 1 fl iv • 3- or 4-factor CCP (prothrombin complex concentrate) iv based on weight, INR and type of CCP, or • Fresh plasma 10–15 ml/kg iv if PCC not available
Direct inhibitors of factor Xa	<p>Activated carbon (50 g) within 2 h of ingestion of dabigatran PCC activated (FEIBA) 50 IU/kg or factor 4 PCC 50 IU/kg iv</p>
Direct thrombin inhibitors	<p>For dabigatran:</p> <ul style="list-style-type: none"> • Idarucizumab 5 g iv (2 vials 2.5 g/50 ml) • Activated carbon (50 g) within 2 h of ingestion (if antidote is not available) • Consider hemodialysis or new dosage of idarucizumab for refractory bleeding for others • PCC activated (FEIBA) 50 IU/kg or factor 4 PCC 50 IU/kg iv
Non-fractional heparin	<p>Protamine 1 mg iv for every 100 IU of heparin administered within the previous 2–3 h (maximum 50 mg in a single dose)</p>
Low molecular weight heparin	<p>Enoxaparin:</p> <ul style="list-style-type: none"> • Supplied within 8 h: protamine 1 mg iv per 1 mg enoxaparin (up to 50 mg in a single dose) • Administered between 8–12 h: protamine 0.5 mg iv per 1 mg enoxaparin (up to 50 mg in a single dose) • Useless after 12 h from administration Dalteparin, nadroparin, tinzaparin • Administered within 3–5 half-lives of heparin: <ul style="list-style-type: none"> – Protamine 1 mg iv per 100 IU heparin (up to 50 mg in a single dose) – rFVIIa 90 mcg/kg iv if protamine is contraindicated

Table 12.18 Continued

First: suspend any antiplatelet/anti-coagulant therapy if it is not absolutely contraindicated	
Antithrombotic	Antidote
Danaparoid	rFVIIa 90 mcg/kg iv
Pentasaccaride	PCC activated (FEIBA) 20 IU/kg or rFVIIa 90 mcg/kg iv
Thrombolytic agents (plasminogen activators)	Cryoprecipitate 10 IU iv Antifibrinolytics (tranexamic acid 10–15 mg/kg iv in 20 min or ε-aminocaproic acid 4–5 g iv) if cryoprecipitate is contraindicated
Anti-aggregant drugs	Desmopressin 0.4 mcg/kg iv If neurosurgical intervention: platelet transfusion

- *Antiepileptics*: not indicated for prevention; for early crises levetiracetam or phenytoin
- *Deep vein thrombosis prophylaxis*: intermittent pneumatic compression, if possible (lower limb trauma) and/or EBPM compatible with the presence or otherwise, and relative severity of haemorrhagic lesions

Figure 12.4 illustrates the management of symptoms related to trauma and highlights a risk factor not considered in previous European panels, namely, the recent past head injury, unusual but easily found in athletes or military where, according to literature data, is a risk factor for definitive brain injury [21–23]. The figure also extends its interest to the follow-up of possible post-traumatic disorders presented by patients who have suffered mild head trauma.

The management of post-traumatic disorders is then completed in Fig. 12.5 where the possible causes of secondary advantage or psychosocial problems at work or in the family are also examined [24, 25].

Figure 12.4 Symptom management. Modified by VA/DoD Clinical Practice Guideline for Management of concussion/Mild Traumatic Brain Injury (mTBI) (https://www.healthquality.va.gov/guidelines/Rehab/mtbi/concussion_mtbi_full_1_0.pdf)

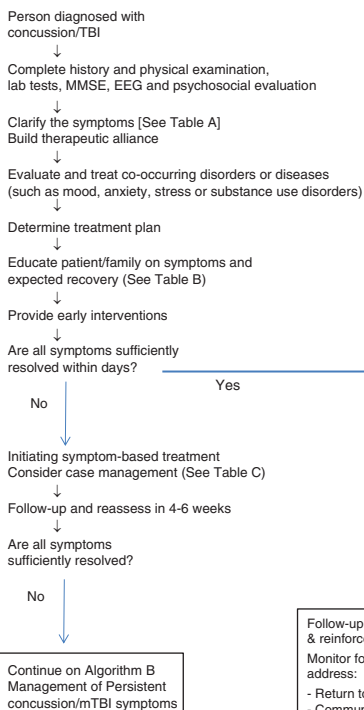


Table A. Symptom Attributes

Duration of symptom
Onset and triggers
Location
Previous episodes
Intensity and impact
Previous treatment and response
Patient perception of symptom
Impact on functioning

Table B. Early Intervention

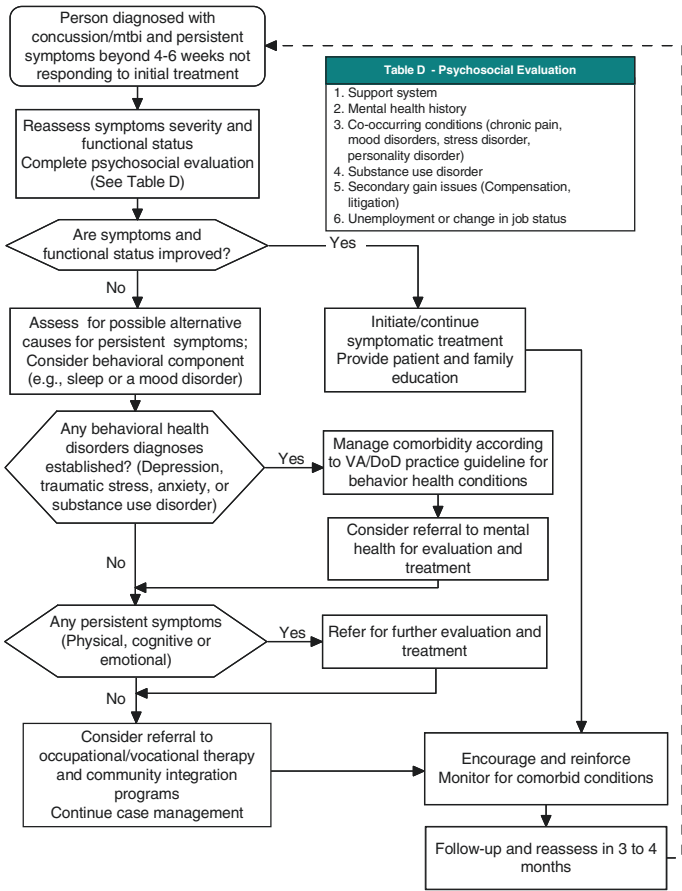
- Provide information and education on symptoms and recovery
- Educate about prevention of further injuries
- Reassure on positive recovery expectation
- Empower patient for self management
- Provide sleep hygiene education
- Teach relaxation techniques
- Recommend limiting use of caffeine/tobacco/alcohol
- Recommend graded exercise with close monitoring
- Encourage monitored progressive return to normal duty/work/activity

Table C. Case Management

- Assign case manager to:
- Follow-up and coordinate (remind) future appointments
 - Reinforce early interventions and education
 - Address psychosocial issues (financial, family, housing or school/work)
 - Connect to available resources

TBI: Traumatic Brain Injury
MMSE: Mini Mental State Examination
EEG: Electroencephalography

Figure 12.5 Follow-up of persistent symptoms. Modified by VA/DoD Clinical Practice Guideline for Management of concussion/ Mild Traumatic Brain Injury (mTBI) (https://www.healthquality.va.gov/guidelines/Rehab/mtbi/concussion_mtbi_full_1_0.pdf)



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13.

Muscle Pain, Weakness and/or Sensory Disorders

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Introduction

Neuromuscular diseases may manifest with **focal or generalized** distribution of reduced strength. Sometimes the diagnosis is delayed because this feature may be due also to a disorder of the central nervous system (see Chap. 10).

Today, it is particularly important to obtain an early diagnosis of a neuromuscular disease because there are increasing possibilities for an early treatment and, consequently, for improving the quality of life of patients [1].

The diagnostic algorithms, included in this chapter, provide a guide for the diagnosis of neuromuscular disorders which can be relevant in an emergency setting. They focus on the main clinical presentations, the onset (from few hours to few days), the presence of associated symptoms and/or signs, the identification of triggering factors and the indications for the most appropriate diagnostic tests.

Considering the different algorithms herein represented, it can be observed that there are several common aspects, because, for example, a patient with muscle weakness with acute onset may be affected either by a disease of a myogenic or neurogenic origin. Particularly, the clinical picture may change according to the presence of an isolated muscle pain or an association with muscle strength deficiency (Table 13.1).

Patient with Acute Onset of Diffuse Muscle Pain

Muscle pain is a frequent and unspecific symptom found in various muscular and extramuscular diseases. In myopathies, myalgia can be present in association with other signs or symptoms such as contractures, fatigue, focal, or diffuse muscle weakness, exercise intolerance, rhabdomyolysis and myoglobinuria. To address the diagnosis in presence of muscle aches, it is important to evaluate [2]:

Table 13.1 Acute muscle weakness: essential clinical notes

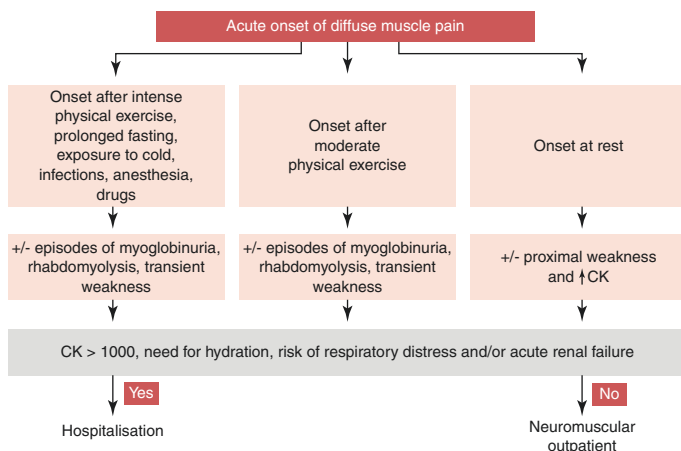
Muscular origin
<ul style="list-style-type: none"> • Proximal, symmetrical, persistent weakness • Usually absence of sensory disturbances • Decreased deep reflexes (especially in districts with utmost weakness) • Recurrent associated aspects: rhabdomyolysis, myoglobinuria, cardiomyopathy • CK level: elevated or very much increased
Neuromuscular junction origin
<ul style="list-style-type: none"> • Weakness of the eye and/or face muscles • Presence of intra-daily fluctuations and fatigability • Absence of sensory disturbances • Normal deep reflexes • CK level: usually normal
Neurogenic origin
<ul style="list-style-type: none"> • Proximal and/or distal muscle weakness, often asymmetrical • Hypotonia, hypotrophy, hypo/areflexia • Possible presence of sensory disturbances • CK level: normal or slightly increased

More about on Neuromuscular Disease Center at Washington University, St. Louis, MO, USA (<http://neuromuscular.wustl.edu/alfindex.htm>)

- The onset at rest, or as a result of triggering factors such as physical exercise, prolonged fasting, fever, exposure to cold, use of medications or general anaesthetic agents.
- The presence of **hyperCKemia** indicating a muscle damage.
- The muscle pain distribution that may be focal, limited to a single muscle district or generalized to involve several muscle groups.
- The association with other signs and/or symptoms as easy fatigue, presence of dark urines ("coca cola-like" = myoglobinuria), proximal muscle weakness or rhabdomyolysis (i.e. muscle necrosis with high serum CK values) [3].

In patients with **muscle pain at rest**, clinical history should carefully evaluate an acquired muscle damage due to drug intake (i.e. statins, antibiotics, neuroleptics) [4] or a coexistence with an extramuscular disease (e.g. autoimmune, neoplastic or infectious diseases). Neurological examination should focus on the presence of muscle weakness with proximal or distal distribution.

Figure 13.1 **Algorithm of the patient with acute onset of diffuse muscle pain**



In patients with **muscle pain after physical activity** (Fig. 13.1), fasting or prolonged exposure to cold, myalgia can occur at four limbs. In these cases, it is important to check the presence of an association with muscle weakness, myoglobinuria and/or rhabdomyolysis [5].

The **need for hospitalization** is mainly related to the risk of respiratory muscles involvement or of an acute renal failure following massive myoglobinuria [6, 7]. In the latter case, forced hydration and, if necessary, dialysis treatment are strongly recommended.

After the acute phase, a timely diagnosis is necessary and includes EMG, muscle MRI, muscle biopsy and biochemical and genetic tests. These investigations can contribute to carry out a correct differential diagnosis between the different forms of myopathies. Since some years, muscle MRI has become a very important diagnostic tool to better define the nature and distribution of muscle involvement, to indicate the biopsy site and to monitor treatment effects [8].

Muscle biopsy remains the mainstay to differentiate genetically determined or acquired myopathies. As regards metabolic myopathies, it may show glycogen storage (muscle glycogenosis),

increased lipid content (lipid storage myopathy) or mitochondrial abnormalities (mitochondrial myopathies) [9] that need to be confirmed by performing specific biochemical and/or molecular genetic tests.

Biochemical assays on muscle homogenates help identify the enzymatic defect and **genetic analysis** reveals the causative mutations. These investigations are important because some metabolic myopathies can be successfully treated with specific drugs. In particular, there are forms of lipid storage myopathies that respond optimally to treatment with riboflavin [10]. The enzyme replacement therapy (ERT) is also available for type II glycogenosis (Pompe disease), which, later in the course of the disease, can develop a respiratory failure [11].

The evidence of inflammatory infiltrates in a muscle biopsy may suggest a diagnosis of inflammatory myopathy, a condition that can be treated successfully with steroids and/or immunosuppressive drugs.

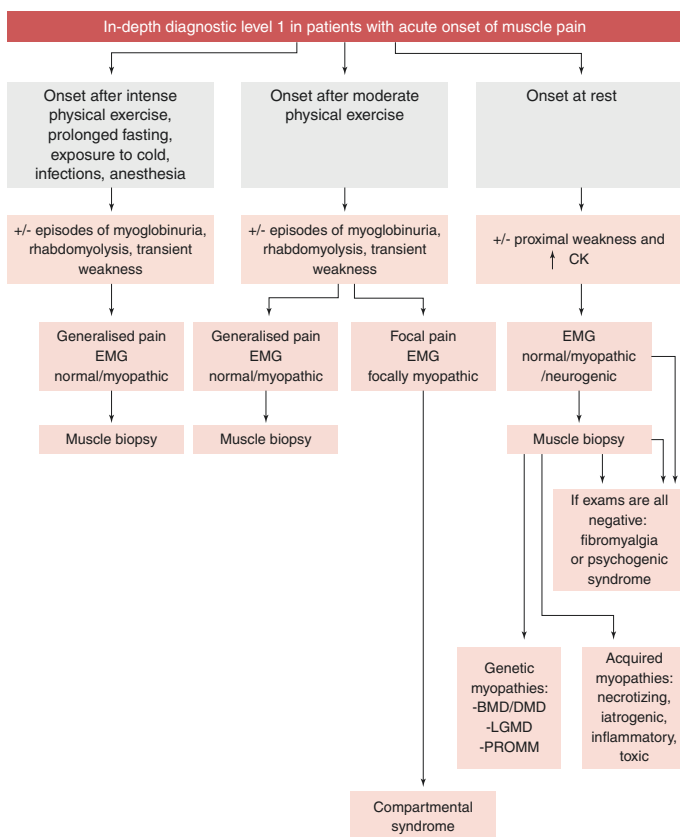
A particular condition is characterized by muscle pain, rhabdomyolysis and acute weakness with a focal distribution (i.e. Anterior tibialis muscle) after a prolonged exercise as in marathon runners ("**compartmental syndrome**"). In such cases, EMG may show focused muscle damage with sparing of other districts [12].

It is necessary to point out that when generalized myalgia is the only symptom, because all diagnostic procedures were negative as CK level, EMG, muscle MRI and muscle biopsy, one should take into account a "**psychogenic illness**" for which a psychiatric investigation must be required.

Finally, it seems appropriate to outline that several patients complaining of intense and diffuse pain, receive the diagnosis of "**fibromyalgia**", a condition, to date, without specific diagnostic criteria [13]. In a certain percentage of patients, fibromyalgia is associated with neuropathy of small fibres.

It is evident from the above considerations that the identification of causes of acute muscle pain requires a multimodal approach in

Figure 13.2 **In-depth diagnostic level 1 in patients with acute onset of muscle pain**



Centres where a full clinical and laboratory workup can be performed. Figure 13.2 summarizes the steps of a first level diagnosis in-depth examination of a patient with acute onset of muscle pain.

If metabolic myopathy is suspected, “**Red flags**” can help to address to different forms (Fig. 13.3), especially using a second-level diagnosis with biochemical and genetic tests (Fig. 13.4).

Figure 13.4 **In-depth diagnostic level 2 in patients with acute onset of muscle pain, hyperCKemia and exercise intolerance**

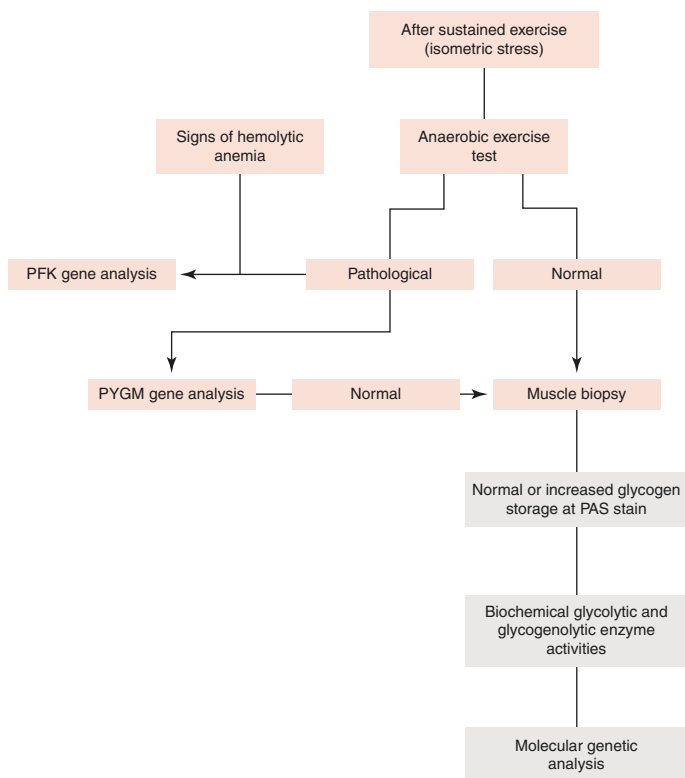
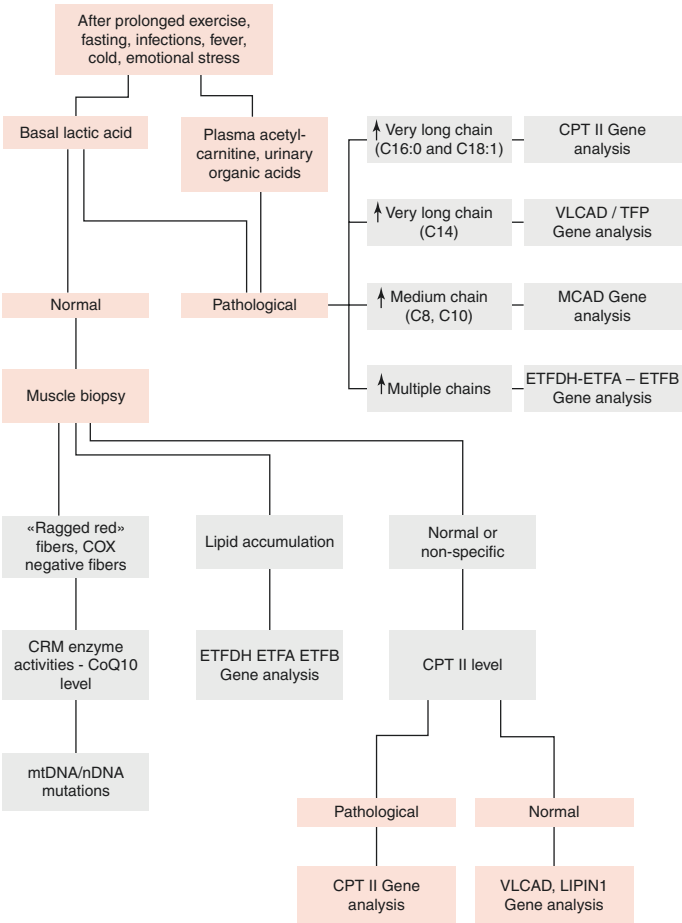


Figure 13.4 Continued



Patient with Generalized Acute Muscle Weakness (Myogenic)

Acute onset of weakness (hours, 1–2 days), due to muscle diseases, is related to a limited number of clinical conditions. Overall, it is important to consider the clinical setting where the patient is

seen (emergency room, intensive care unit, medical wards) and to evaluate:

- Distribution of weakness (generalized or focal)
- Persistent or possible fluctuations of symptoms
- Involvement of eye and/or lower facial muscles
- Association with myalgia, fever, skin lesions
- Potential triggering factors of symptoms

The algorithm has been set up to be suitable in emergency/urgency conditions. A first, important distinction has been made between weakness occurring at rest (Fig. 13.5) and during or after physical activity (Fig. 13.6).

The cases with **muscular weakness appearing at rest** have been divided into two categories: cases with normal CK and with increased CK.

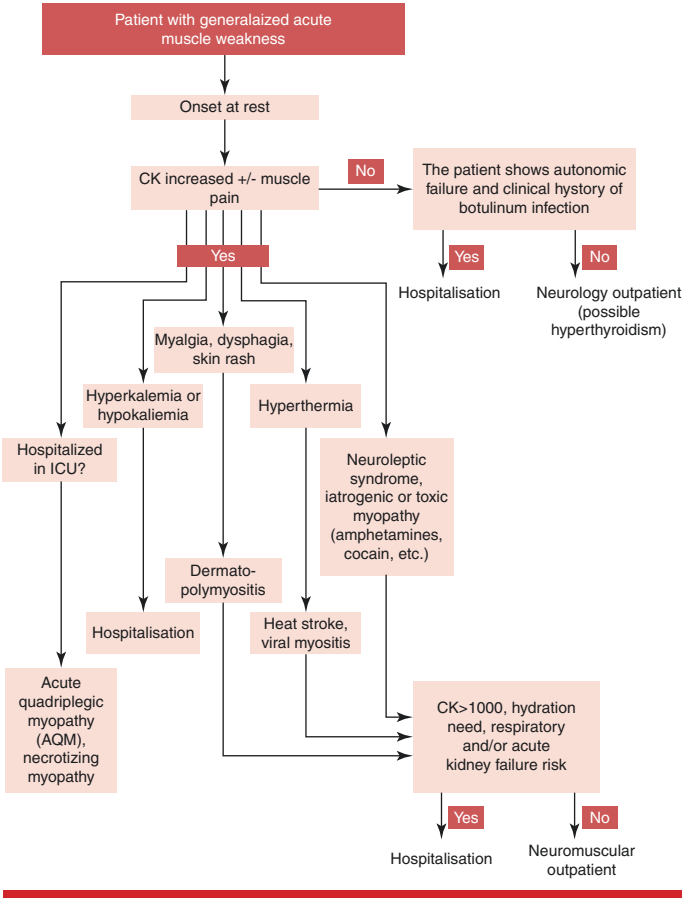
A patient may experience **acute weakness with normal CK**; in this case, the dosage of thyroid hormones is important and may lead to a diagnosis of hyperthyroidism.

An accurate clinical history (presence of skin injuries, drug abuse, etc.), presence of dysautonomia and a complete neurophysiological study with repetitive stimulation or single fibre examination, can lead to diagnosis of “**botulism**”.

When **muscle weakness is associated with increased CK**, the scenario becomes more complex.

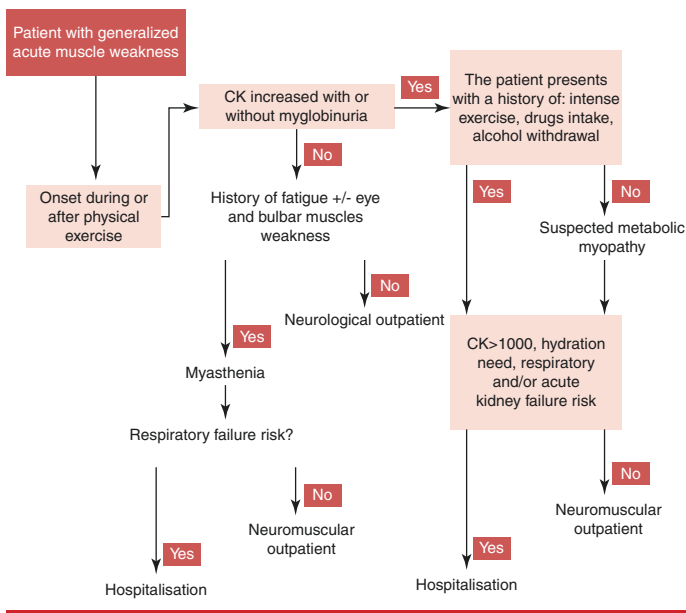
For example, if a patient in the emergency room shows a subacute onset (hours) of generalized weakness causing flaccid paraparesis or tetraparesis without involvement of respiratory muscles, a quick determination of plasma ions may conduct to the diagnosis of **hypokalemic or hyperkalemic paralysis** (there are genetic forms and acquired forms). Acquired causes of hypokalemia include chronic diarrhoea, prolonged use of diuretics, hyperaldosteronism, excessive liquorice, coffee or tea intake. The detection of elevated levels of thyroid hormones can lead to the diagnosis of hypokalemic paralysis by thyrotoxicosis [14].

Figure 13.5 **Algorithm of the patient with generalized acute muscle weakness with onset at rest**



Muscle weakness with altered potassium concentrations is also found in some genetic forms called “**channelopathies**”. The diagnosis of **periodic hypokalemic paralysis** is based on a history of episodes of flaccid paralysis, lasting from hours to days, triggered by food rich in carbohydrates, alcohol intake or glucose infusions

Figure 13.6 **Algorithm of the patient with generalized acute muscle weakness, arising during or after physical activity**



with evidence of hypokalemia during attacks and absence of both clinical and EMG myotonia. Fournier's test has proved to be a very useful diagnostic tool in the differential diagnosis with other myopathic forms [15].

The diagnosis of **periodic hyperkalemic paralysis** is made in presence of attacks of flaccid paralysis that can be associated with weakness of eye muscles, swallowing and trunk muscles, hyperkalemia (>5 mmol/l), onset before the age of 20. It can be triggered by an excessive intake of food rich in potassium after rest or exercise, glucocorticoids, exposure to cold or emotional stress. **The cardiac risk generated by hyperkalemia or hypokalemia requires a "red code" in the emergency room.**

If muscle weakness is associated with **increased CK, myalgia, dysphagia, recurrent skin rash**, an **“inflammatory myopathy”**, as polymyositis or dermatomyositis should be suspected [16]. These patients are initially seen by internists, rheumatologists, dermatologists, whereas the neurologist is consulted later. In elderly patients, inflammatory myopathies can be paraneoplastic and requires a very accurate workup. Diagnostic confirmation of inflammatory myopathy is often obtained by histological, histochemical and immunohistochemical studies of muscle biopsy samples.

In **presence of fever**, a **viral myositis** should also be considered. In these cases, in addition to symptoms (myalgia) and signs of myopathy (muscle weakness), there are often other aspects related to a systemic disease. The involved viruses are different as influenza type A and B (most frequent), enterovirus, EB, adenovirus and HIV. Myositis due to these viruses is characterized by the sudden onset, usually in the first days of convalescence, of myalgia at lower limbs with difficulty in walking. EMG shows myopathic signs; in these cases, there are no indications for a muscle biopsy, the treatment is symptomatic [16] and the disease resolves in few days [17].

Additional cause of acute weakness are body-temperature changes as observed in heat stroke, malignant hyperthermia, neuroleptic syndrome or after intake of some toxic substances (amphetamines, cocaine, etc.). Muscle damage can be so massive that **myoglobinuria appears and can be a threatening sign that needs to be rapidly treated**.

In the **intensive care unit (ICU)**, an acute onset of muscle weakness can be observed in patients with [18] **“acute quadriplegic myopathy”**. This condition was initially observed in asthmatic patients treated with non-depolarizing steroids and neuromuscular blockers and was later reported in patients with organ transplantation. The clinical picture is characterized by a severe weakness of all voluntary muscles, prevailing at the proximal districts. Weakness of respiratory muscles hinders weaning patients from ventilatory support [19]. Muscle biopsy may show the loss of myosin filaments. Other patients may have massive myonecrosis as the **acute**

necrotizing myopathy with vacuolizations and phagocytosis of muscle fibres.

Other cases of subacute onset of muscle weakness with high CK are described in patients taking **some medications** like antipsychotics and antidepressants, hypnotic sedatives, antihistamines, chemotherapies and lipid-lowering drugs (i.e. **Statins**). The muscle disorder could also be caused by concomitant use of more drugs together, likely for a synergistic effect [4].

Muscle weakness that appears during or after **physical activity** (Fig. 13.6) may be or not associated with myoglobinuria. Some causes of **myoglobinuria** could be excessive muscle activity as in marathon runners, convulsions, or alcohol withdrawal syndrome.

Metabolic myopathies due to enzyme defects (i.e. carnitine palmitoyltransferase deficiency, myophosphorylase deficiency, phosphofructokinase deficiency, respiratory chain enzymes deficiency) may present with myoglobinuria.

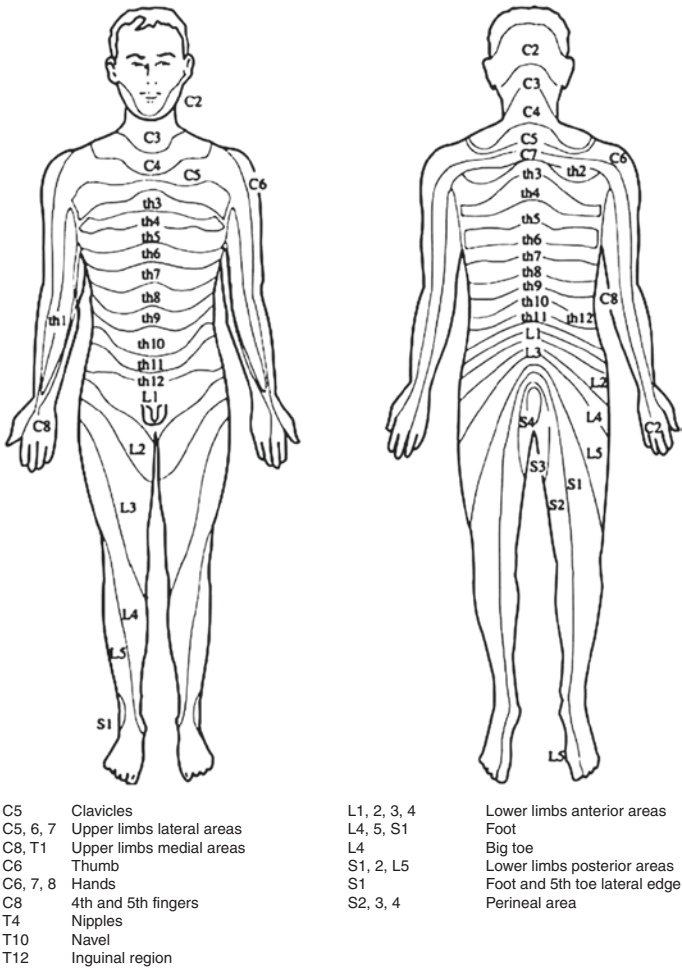
Finally, we must remember the possible acute onset of **myasthenia**.

Patient with Acute Muscle Weakness (Neurogenic and Non-traumatic)

The classification of the diseases of peripheral nervous system is characterized by a clinical heterogeneity. On a practical level, it is useful to adopt the criterion of the clinical distribution, distinguishing focal forms from diffuse neuropathies. Analysis of any associated or isolated sensory disturbances and their distribution will provide additional diagnostic data (Fig. 13.7).

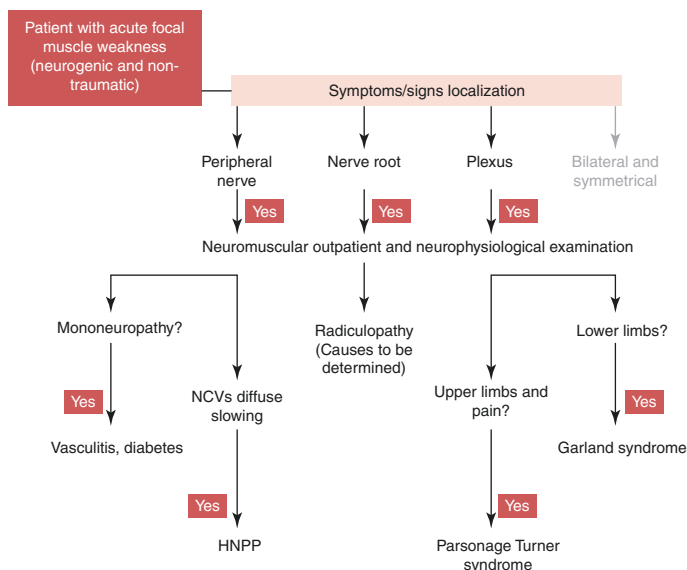
The evaluation of the somatic distribution of symptoms and signs is essential for a correct diagnosis of impairment of a single nerve, one or more roots or plexus. However, these patients should be referred to a neuromuscular centre to perform a complete clinical and neurophysiological examination (Fig. 13.8).

Figure 13.7 Skin dermatomers



On the other hand, if, after an acute onset, the distribution of symptoms/signs is bilateral and symmetrical or more rarely asymmetrical, the patient should always be hospitalized because of a possible respiratory involvement [20] (Fig. 13.9).

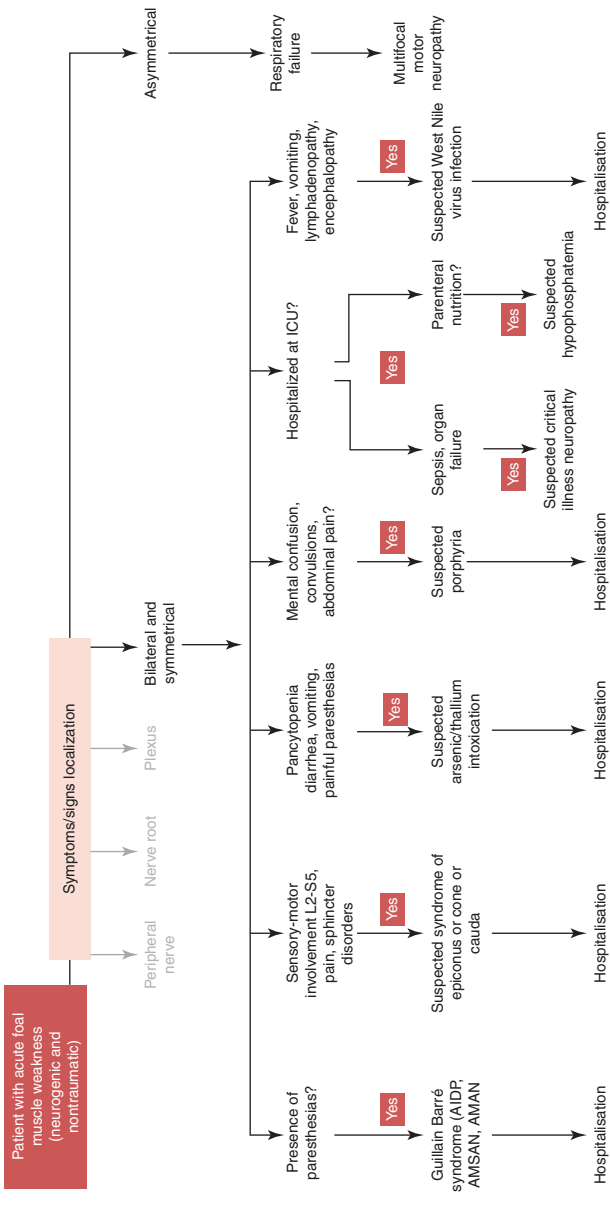
Figure 13.8 **Algorithm of the patient with acute focal muscle weakness (neurogenic and non-traumatic)**



There is no doubt that **Guillain-Barré syndrome** (GBS) is the most frequent cause of acute weakness of neurogenic origin. If suspected on anamnestic data (a previous respiratory or intestinal infection is frequently reported), the patient must be admitted to the hospital and submitted to clinical, electrophysiological and cerebrospinal fluid examinations [21]. The neurophysiological investigations must sometimes be repeated after a few weeks to specify the demyelinating or axonal degenerative nature of the disease. Hospitalization is also advised because 20% of patients may experience a respiratory muscle involvement and need intensive care [22, 23].

Another possible problem requiring hospitalization is paroxysmal dysautonomia with a variable percentage between 1/3 and 2/3 of GBS patients [24, 25]. Acute-onset muscle weakness is much less frequent, sometimes with pain (with mostly distal and asymmetric involvement in the upper limbs), but can be

Figure 13.9 Algorithm of the patient with diffuse acute muscle weakness (neurogenic and non-traumatic)



observed in multifocal motor neuropathy associated with multiple blocks of nerve conduction, rarely with involvement of the phrenic nerve.

In cases of acute neuropathy, a diagnosis of **porphyria** has to be considered [26]. This diagnosis could be missed because of its complex clinical manifestations similar to other pathologies. The most frequent variant is the **acute intermittent porphyria**, with autosomal dominant transmission, low penetration and prevalence between 1 and 10 per 100,000. The most frequent manifestations are acute abdominal pain associated with nausea, vomiting and agitation. In some cases, initially, there is also pain in the back, likely diffusing to lower limbs, with a rapid evolution towards a severe neuropathy, mainly motor and autonomic with possible involvement of respiratory apparatus [27]. Facial and bulbar impairment is often present, whereas tendon reflexes are generally absent, with preservation of Achilles tendons reflexes. The strong similarity of such a clinical picture with a GBS is evident; the **differential diagnosis** must be based on the clinical history (possible triggering factors), on the presence of family history and biochemical investigations (dosage of porphobilinogen and delta-aminolevulinic acid in the urine). A simple test that can be useful is the dark colouring of urine when exposed to the sun (polymerization of excessive porphobilinogen). Early diagnosis is crucial for the patient's life, as it will be possible to identify events or trigger factors; in case of seizures, the administration of barbiturates has to be avoided!

Acute heavy metal intoxications (arsenic and thallium) are excellent examples of the rule that neurotoxic substances are rarely selective for the central nervous system. In fact, the clinical picture is characterized by the simultaneous or sequential involvement of several organs. This is a relevant clue for an early differential diagnosis. Both thallium and arsenic are contained in pesticides, and their accidental intake is possible. In both cases, the clinical phase preceding the neuropathic phase is characterized by gastrointestinal (diarrhoea, nausea, vomiting) and autonomic (tachycardia and hyper/hypotension) symptoms. The neuropathic aspects, which occur immediately afterwards, are initially sensitive with burning paraesthesias and dysto-proximal diffusion, rapidly

followed by progressive weakness which could also lead to respiratory failure [28, 29].

The acute onset of weakness can also affect **patients with other diseases** and complicate the clinical picture. In fact, quite often, patients in ICU, develop acute myopathy and/or neuropathy (critical illness neuro-myopathy) [19]. Neuromuscular involvement is usually detected when difficulty in weaning the patients from artificial ventilation emerges. In fact, neuromuscular symptoms have already arisen, but, given the critical condition of patients, it could be difficult to detect them. Early diagnosis is important to avoid prolonged hospitalization in ICUs and to improve long-term recovery. Clinically, since patients manifest often with severe quadriplegia or tetraparesis, it is important to control the respiratory capacity. Electrophysiological monitoring, which in critical patients shows an early drop in the amplitude of CMAPs and sensory potentials (SAPs), can be a valuable aid. Risk factors for the onset of **critical illness neuro-myopathy** have been identified, such as sepsis, multiple organ failure, use of steroids and/or neuromuscular blockers, prolonged immobility and hyperglycaemia [30]. The disease is attributed to axonal degeneration induced by systemic inflammatory reaction with microvasculitis. It has also been suggested a transient inexcitability of sodium voltage-dependent channels with consequent functional paralysis of axons and muscle fibres [31]. **Phosphatemia** (insulin shifts phosphates within cells) should also be closely monitored to avoid the onset of an areflexic tetraparesis, which, although rather rare, should be considered in the differential diagnosis of critical illness, in patients recently operated or on prolonged parenteral nutrition [32]. In cases of severe hypophosphatemia, confusion, convulsions, encephalopathy and coma can also be observed. More frequently, the clinical picture consists of a rapid evolution of perioral and limb paraesthesias, as well as the presence of dysarthria and tetraparesis.

West Nile fever is a disease caused by the West Nile virus. The reservoirs of the virus are wild birds and mosquitoes, whose stings are the main vectors of transmission to man. The incubation period from the time of the infected mosquito bite varies between 2 and 14 days but can also be as long as 21 days in subjects with immune system deficiencies. Most infected people do not initially show any symptoms, but, among the symptomatic cases, about 20% have

mild symptoms fever, headache, nausea, vomiting, enlarged lymph nodes and skin rashes. Acute flaccid paralysis is identical to poliovirus paralysis and can rapidly lead to respiratory failure. The most serious symptoms occur in less than 1% of infected people and include high fever, severe headaches, muscle weakness, disorientation, tremors, visual disturbances, numbness, convulsions, up to paralysis and coma. Some neurological effects can be permanent or lethal; in the most serious cases (about one in a thousand), the virus can cause lethal encephalitis. The diagnosis is recognized mainly through laboratory tests (Elisa or immunofluorescence) carried out on serum and, where indicated, on cerebrospinal fluid for the detection of IgM antibodies.

If the motor deficit is limited to the lower limbs with sensory deficit, pain and sphincter disorders, one must also suspect a **syndrome of epiconus, cone and cauda**.

Patient with Acute Sensitivity Disorder (Peripheral Type)

Acute, non-traumatic sensory disorders can also be distinguished by their distribution into “focal” and “diffuse”. “Focal” disorders also include those with multifocal distribution, since they recognize similar pathogenic mechanisms (Fig. 13.10).

The distinction between **acute focal/multifocal and diffuse sensory disorders** is essentially based on clinical aspects. On the other hand, no additional diagnostic tools are normally available at emergency room [33].

Subsequently, the differential diagnosis between forms involving one or more nerves, one or more roots or a portion of the plexus, of one or both sides, in the context of diffuse disorders, between forms with motor dysfunction or without motor dysfunction, is based on clinical suspect and/or neurophysiological evaluation. Figure 13.11 summarizes the steps of clinical and neurophysiological investigations of the patient with acute sensory disorder and focal distribution.

Figure 13.10 Patient algorithm with acute sensory disorder (peripheral)

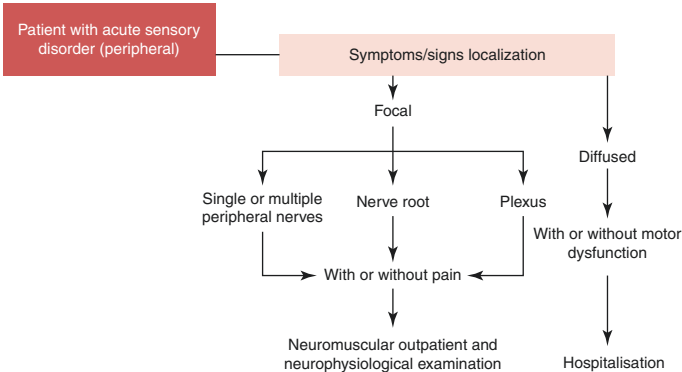
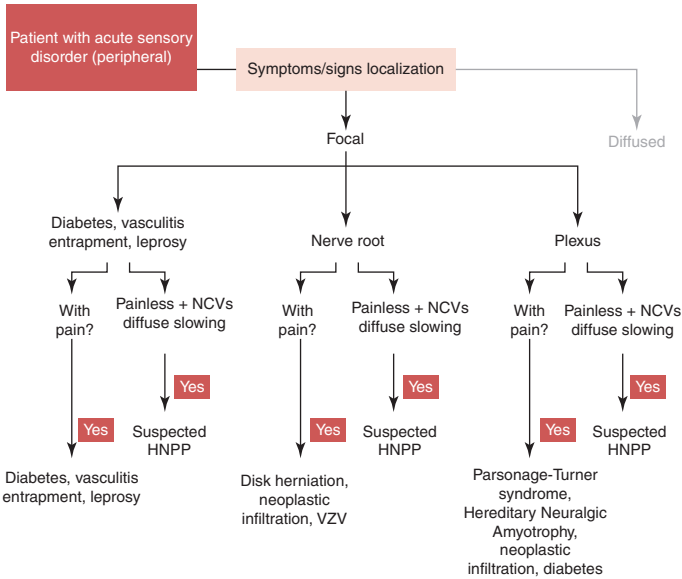


Figure 13.11 In-depth clinical-neurophysiological diagnosis of the patient with acute sensory disorder and focal distribution

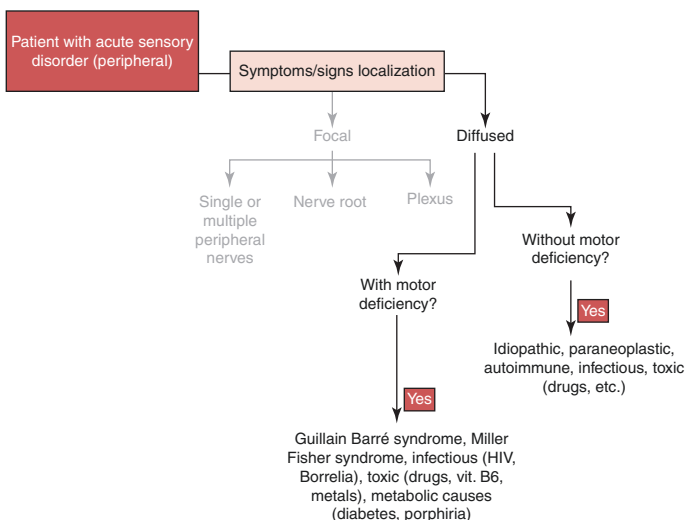


Focal forms should be distinguished according to **presence or absence of pain**. In fact, acute sensitivity disorders due to compression, trauma or vasculitic involvement of one or more nerves, compression or infiltrative lesions of one or more nerve roots and plexus lesions on an autoimmune, vasculitic or genetic basis are usually accompanied by a variable degree of **pain or other related symptoms of a motor nature**.

In contrast, **pain is** typically **absent** in hereditary neuropathies with increased susceptibility of the nerves to compression damage (HNPP). HNPP typically manifests with acute sensory disorders (hypoesthesia and/or paraesthesia) and distribution in the territory of one or more nerves or roots or plexus. HNPP may also be associated with symptoms or motor signs.

Diffuse acute sensory disorders recognize a different pathogenesis if they are associated or not with symptoms and/or signs of motor dysfunction. This can be established, once again, based on clinical and neurophysiological studies. In the first case (with motor dysfunction), acute disimmune forms such as Guillain-Barré syndrome and Miller Fisher syndrome are the most common. The latter is characterized by the presence of ataxia, areflexia and ophthalmoparesis (which is the main motor dysfunction) [34]. In the differential diagnosis (Fig. 13.12), other hypotheses are reported in cases of acute sensory disturbances with variable degree of motor dysfunction [35]. Then, there are some types where, by definition, there are no symptoms and motor signs and they may present with an acute onset (even if they are sometimes subacute or more rarely chronic) [36].

Figure 13.12 In-depth clinical-neurophysiological diagnosis in patients with acute sensory disorder and diffuse distribution



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14.

Movement Disorders Emergencies

Carlo Colosimo, Francesca Galletti, Giovanni Cossu,
Roberto Marconi, and Roberto Eleopra

Introduction

The concept of movement disorders emergencies has been introduced to describe all those conditions in which the clinical picture is an acute or subacute evolution of the movement disorder in which a diagnostic delay can cause severe clinical consequences, including death. Both parkinsonian-type hypokinetic disorders and various hyperkinetic forms can, indeed, have an acute onset and present in aggressive form (Fig. 14.1). At the same time, sudden

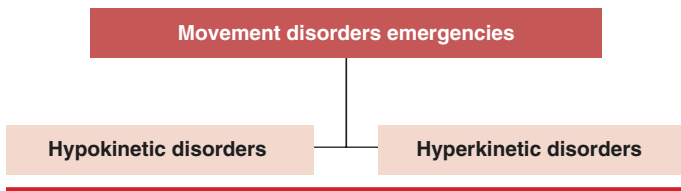
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Figure 14.1 **Movement disorders emergencies**



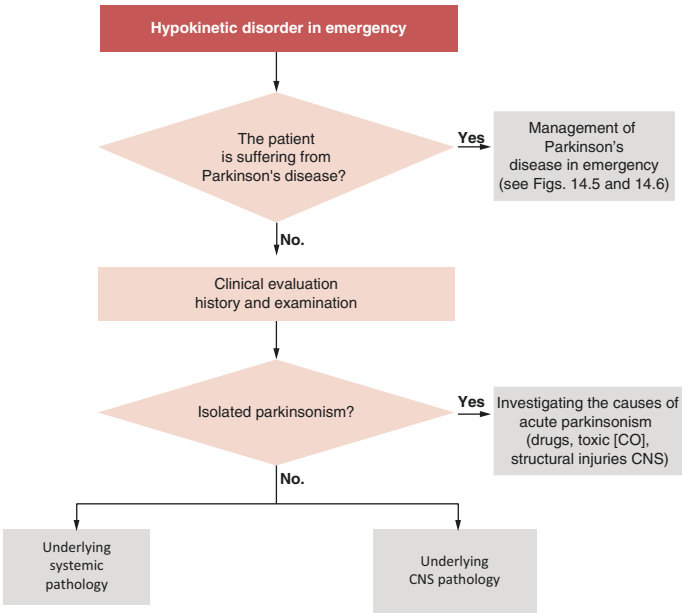
severe complications of chronic diseases, such as Parkinson's disease or dystonia, may also occur [1].

The timely classification of a hypokinetic disorder (slowing down or complete movement blockage) or hyperkinetic disorder (characterized by the presence of involuntary movements) of new onset, as well as the abrupt exacerbation of a known movement disorder, is of great importance. These pictures, in fact, may represent an early symptom of an encephalopathic condition supported by a systemic extra-neurological disorder of which it may allow a correct diagnosis [2]. On the other hand, even the sudden exacerbation of a known disorder may require urgent intervention [3].

Hypokinetic Disorders

Hypokinetic disorders are characterized by the presence of bradykinesia and rigidity. The management of these symptoms, in emergency, requires, first of all, to exclude whether a patient is suffering from Parkinson's disease or from a known form of parkinsonism, and if specific conditions related to the basic pathology can justify access to the emergency rooms (Fig. 14.2). In all other cases, it is necessary to rule out conditions predisposing to acute parkinsonism, which may occur alone or accompanied by other signs and symptoms of neurological impairment or systemic alteration [1].

Figure 14.2 **Emergencies in hypokinetic disorder: PD and other parkinsonian forms**



Patient Without Parkinson's Disease

Signs and Symptoms for Differential Diagnosis

Acute onset of an isolated parkinsonism is a rare occurrence, and, in most cases, it is secondary to exposure to toxic substances [2]. Cases associated with cyanide, manganese, methanol poisoning, and exposure to carbon monoxide and organophosphates have been described [4–6]. These elements can indeed induce acute damage to the basal ganglia. An acute parkinsonism associated

with other signs and symptoms of central nervous system impairment may rarely manifest in some forms of encephalitis, such as the lethargic one, in intracranial masses and after acute cerebrovascular events [7, 8]. However, in such cases, parkinsonism generally occurs weeks/months after the occurrence of the offending cause than in an acute phase.

The presence of acute parkinsonism associated with demyelinating pontine alterations in MRI must always lead to the suspicion of 'central pontine myelinolysis' [2].

In 0.2% of patients who have taken neuroleptics, a **malignant neuroleptic syndrome** may occur. Neuroleptic malignant syndrome worsens in the first 48–72 h and may persist for days. It is associated with a mortality rate of 5–20% [9]. Intoxication by substances that enhance serotonergic neurotransmission may, however, induce a **serotonergic syndrome** [10]. Two further pictures that come under differential diagnosis with neuroleptic malignant syndrome are lethal catatonia and malignant hyperthermia. The first condition can occur in the context of severe forms of psychosis, while malignant hyperthermia is due to the administration of anaesthetics and is rarely found in emergency rooms [2].

Clinical Evaluation

History: Within the diagnostic-therapeutic course of a patient with an acute hypokinetic disorder in emergency, history plays a crucial role (Table 14.1). It must be investigated whether:

- The patient has Parkinson's disease or a known parkinsonian syndrome.
- The patient has been exposed to environmental toxins or may have taken toxic substances (where the patient has spent the last few hours? Other people have presented the same clinical picture? Has he/she other systemic symptoms?).
- The patient takes medications? (type of substances recently added and any dosage changes, also considering a possible self-medication by the patient).
- The patient has comorbid diseases (e.g. a psychiatric disorder, respiratory, thyroid, or liver diseases).

Table 14.1 Differential diagnosis of acute-onset parkinsonism

Clinical pictures	Signs/symptoms	Red flags
Carbon monoxide/ methanol poisoning [4–6]	Apathy, loss of psychic self-activation, acute akinesia, marked difficulty in walking Presence of symptoms in the target organs of the substance in question	Where and how you spent your last hours? The people who were with him presented the same symptoms?
Encephalitis (e.g. lethargic encephalitis), intracranial masses, acute cerebrovascular events [7, 8]	Acute parkinsonism Other CNS signs	Most frequently in weeks/ months
Malignant neuroleptic syndrome [9]	Impairment of consciousness Diffuse rigidity Bradykinesia Fever (up to 39 °C) Autonomic disorders (tachycardia, tachypnoea, alterations in blood pressure) HyperCKemia (also >1000 IU/l) Leucocytosis	Young adults Male sex recent start (2–3 days) or change in neuroleptic therapy Therapy with: haloperidol, fluphenazine, chlorpromazine
Serotonergic syndrome [10]	Alterations of consciousness Rigidity Fever Autonomic disorders Myoclonus and epileptic seizures HyperCKemia (minor compared to neuroleptic malignant syndrome)	Development over days Simultaneous intake of several serotonergic drugs: serotonin reuptake inhibitors, type B monoamine oxidase inhibitors, tricyclic antidepressants, triptans Intake of substances of abuse (cocaine, amphetamines)
Lethal catatonia [2]	Rigidity Catatonic postures	Positive history of psychotic disorders

Physical Examination

- Vital parameters (body temperature, heart rate, and respiratory rate): their importance is crucial to distinguish acute parkinsonism from a malignant neuroleptic syndrome or serotonergic syndrome.
- Neurological examination:
 - Rigid hypertonia, with usually generalized distribution. If, on the other hand, contracture and/or rigidity is observed in more localized districts, it should be considered, alternative diagnosis like tetanus (in which a typical involvement of the masticatory muscles and limbs is generally observed) to stiff man's syndrome (in which the paravertebral muscles of the lumbar spine and proximal muscles of the lower limbs are generally involved) [11].
 - Hyperkinesia, mainly of myoclonic type, typically in serotonergic syndrome.
 - Bilateral mydriasis in serotonergic syndrome.
 - Other signs and symptoms of central nervous system impairment: secondary forms of encephalitis or acute cerebrovascular events.

Diagnostic Procedures

- Laboratory tests:
 - Blood cell count: detection of leucocytosis in neuroleptic malignant syndrome or secondary forms of infectious diseases
 - Liver function: increased transaminases in malignant neuroleptic syndrome
 - Renal function: altered by neuroleptics in malignant syndrome
 - CPK and other muscle enzymes: increased in neuroleptic malignant syndrome and, to a lesser extent, serotonergic syndrome
 - Electrolytes: sometimes a picture of severe hypocalcaemia can induce widespread contractures, which can mimic stiffness, or cause a choreic syndrome
 - Toxicological examination: also by carrying out specific tests when the risk of exposure to toxins is high
- Haemogasanalysis: determination of carboxyhaemoglobin to exclude forms of parkinsonism on a toxic basis

- Structural neuroimaging: the presence of signal alterations in the midbrain and basal ganglia compatible with vascular, toxic-dysmetabolic, or inflammatory pathology must essentially be excluded

Treatment

In front of a patient with an acute hypokinetic disorder in the emergency room, it is necessary to proceed with hospitalization, for clinical observation and to establish timely treatment.

The identification of a toxic substance must prompt its immediate interruption, as well as the diagnosis of underlying diseases that may require specific treatment.

With regard to specific situations, such as neuroleptic malignant syndrome and serotonergic syndrome, intensive care monitoring, withdrawal of the offending drugs, adequate hydration, and, possibly, the administration of specific drugs such as dopaminergic agonists by parenteral or transdermal route, or serotonergic antagonists are necessary (Fig. 14.3).

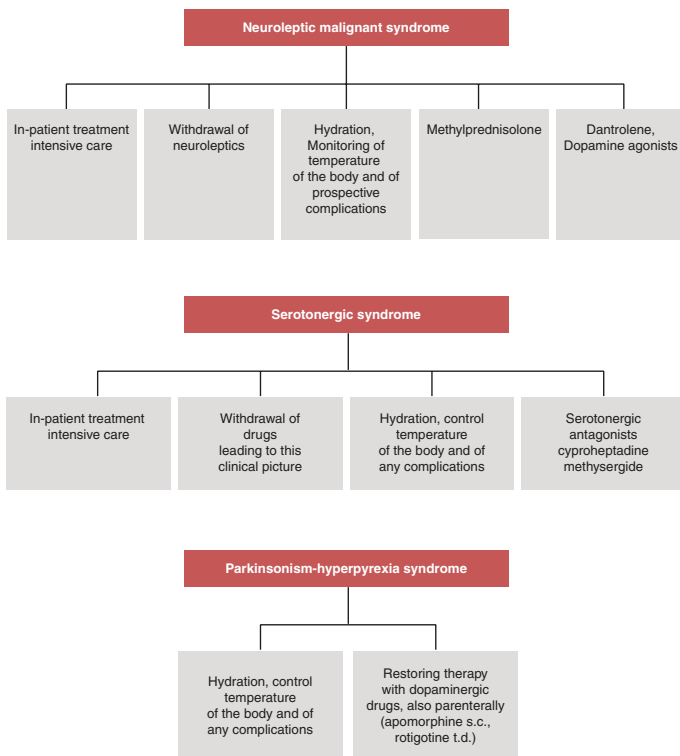
Patients with Parkinson's Disease

Several studies have documented that about 35–60% of patients with Parkinson's disease have access to emergency room [12, 13] for several causes (Table 14.2, Fig. 14.4). However, the duration of the disease and the severity of motor disability are not related to the frequency of accesses [3].

Patients in a severe 'off' state or with *parkinsonism/hyperpyrexia syndrome* may experience rapid complications such as acute renal failure, *ab ingestis* pneumonia, venous thromboembolism, and disseminated intravascular coagulation. Mortality is as high as 4% of cases [17].

Postural instability, *freezing* of gait, and orthostatic hypotension are causes of falls in parkinsonian patients (Fig. 14.5). Approximately 70% of patients have at least one fall per year [19]. Dysphagia,

Figure 14.3 Treatment of acute hypokinetic disorders



frequently found in advanced stages of the disease, can lead to *ab ingestis* pneumonia and, consequently, respiratory tract infections. On the other hand, frequent urinary tract dysfunctions in such patients predispose to infectious events. Infections can interfere with motor function and, therefore, the intervention of the specialist becomes decisive for an adjustment of the therapeutic regimen. Psychiatric disorders are among the most frequent non-motor symptoms associated with Parkinson's disease (Fig. 14.6).

Table 14.2 Parkinson's disease

	Clinical pictures	Signs/symptoms	Red flags
Neurological complication	Severe off [2] status	Akinesia Rigidity	Abrupt reduction? Withdrawal?
	Parkinsonism/hyperpyrexia [14, 15]	Akinesia Rigidity Fever Alterations in the state of consciousness Autonomic disturbances CPK increase	Non-dopaminergic therapeutic changes? Deep brain stimulation surgery [16]?
	Clinical pictures	Symptoms/consequences or locations concerned	Red flags
Non-neurological complications [14]	Falls [19]	Cranial trauma pelvis/limb fractures	History of falls? Pain? Abnormal limb posture?
	Infections	Respiratory tract urinary tract	Dysphagia? Urgency? Dysuria? Nocturia? Paradox Iscuria?
	Psychiatric disorders	Disperceptive phenomena (illusions, visual hallucinations) Delirium (paranoid and of jealousy)	Therapeutic changes? Dehydration? Metabolic disorders? Infectious complications?

Clinical pictures leading to emergency hospitalisation

Figure 14.4 Hyperpyrexia

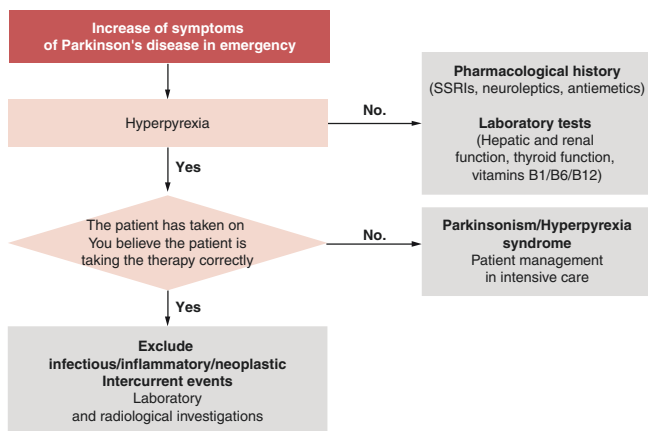


Figure 14.5 Falls

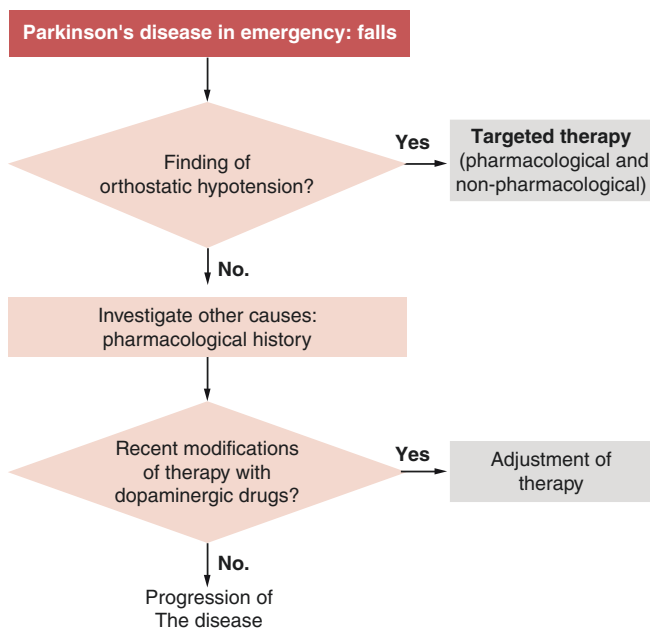
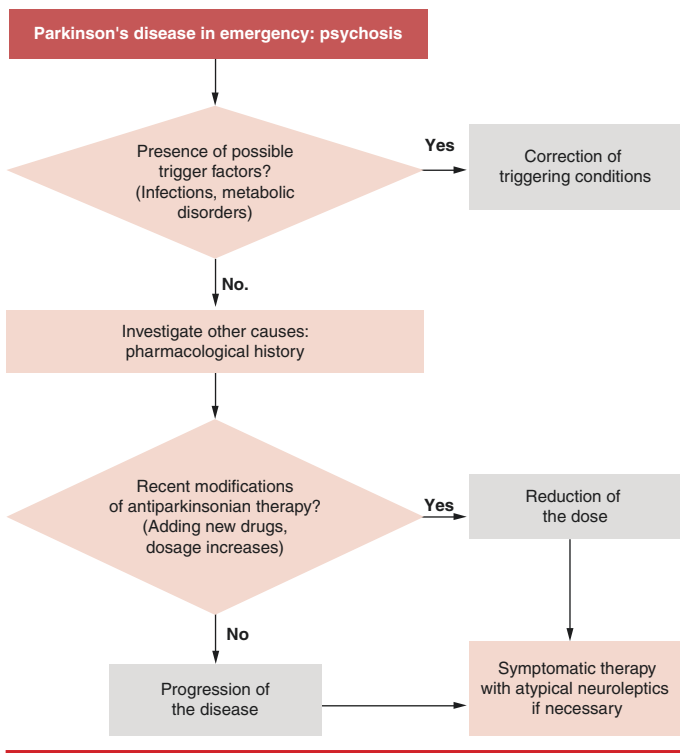


Figure 14.6 **Acute psychosis in Parkinson's disease**

Treatment

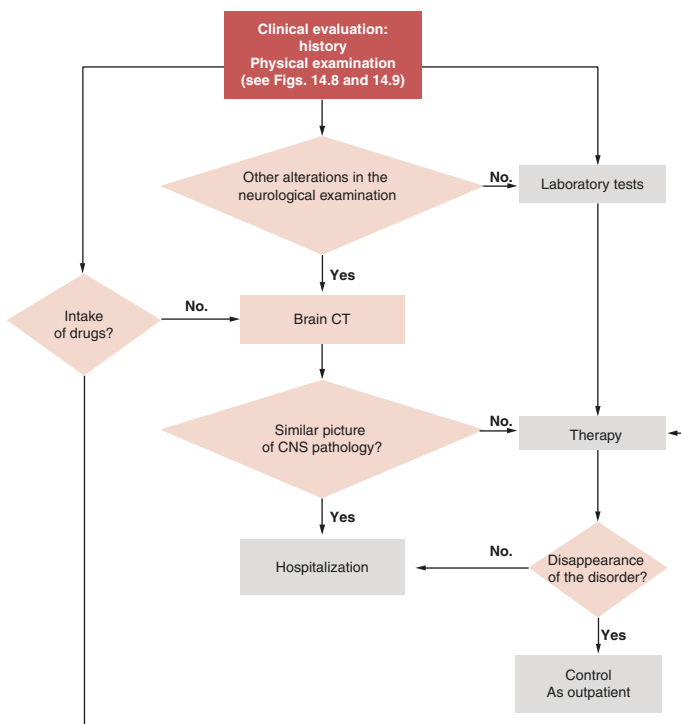
- Severe forms of 'off' or parkinsonism-hyperpyrexia syndrome:
 - Immediate restoration of dopaminergic therapy, also by means of a nasogastric tube, in addition to supportive measures. In special cases, when enteral administration is not possible, apomorphine infusion can be used subcutaneously via serial boluses or infusion pump [2, 3].
 - The use of high doses of methylprednisolone has been proposed [18].
- Psychiatric disorders:
 - Correction of all precipitating conditions.
 - Interruption of therapies with a possible psychoaffective effect.

- ❑ Adjustment of the dose of dopaminergic therapy, without affecting motor performance.
- ❑ If neuroleptic therapy is indicated, clozapine and quetiapine are the first choice.

Hyperkinetic Disorders

Signs and symptoms for differential diagnosis: hyperkinetic disorders are common in the emergency setting (Fig. 14.7), as they can have an acute onset, suddenly complicate the course of systemic diseases, or represent the adverse event of drug therapy [20].

Figure 14.7 Emergencies in hyperkinetic disorders



The diagnostic-therapeutic approach to hyperkinetic disorders cannot be separated from a clinical distinction of the different phenomenological pictures (Table 14.3, Fig. 14.8) [21].

Table 14.3 Differential diagnosis of hyperkinetic disorders

Clinical picture	Characteristics of the involuntary movement	Peculiarity
Chorea	Irregular, afinalistic, abrupt onset, short-lasting. Expression of a random activation of several muscle districts	The patient may partially suppress these movements or incorporate them into a predominantly finalistic activity
Ballism	Abrupt, rapid onset, sometimes violent, and large amplitude involves proximal limb muscles Can mimic the gesture of throwing an object	Frequently only one side of the body is affected
Athetosis	Slow and subcontinuous, stereotyped	Predominantly flexo-extension of the distal joints of the limbs
Positive myoclonus	Involuntary contraction and arrhythmic of one or more muscles Sudden onset Very short duration	
Negative myoclonus	Abrupt interruption of the contraction of one or more muscles involved in maintaining a posture	
Dystonia	Involuntary co-contraction of agonist and antagonist muscles	Execution of repetitive torsional movements Assumption of abnormal, schematic, predictable postures, always in the same direction, aggravated or delayed by the execution of tasks or actions They can be improved with the so-called geste antagoniste
Myokymia	Contraction of a certain number of motor units	Visible as continuous waves when observing the affected muscle segment

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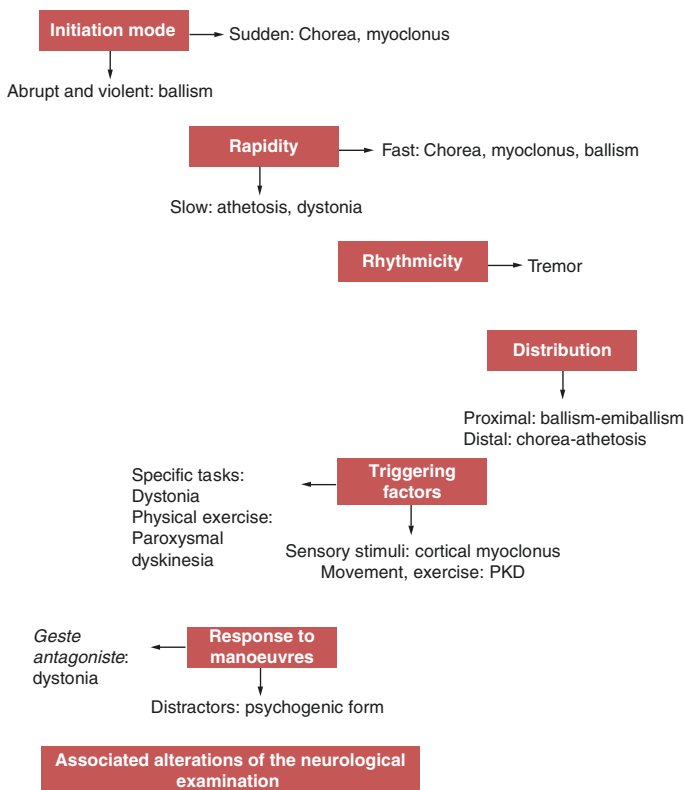
Table 14.3 Continued

Clinical picture	Characteristics of the involuntary movement	Peculiarity
Tremor	Involuntary movement, oscillatory type, around an axis, characterized by a symmetrical amplitude in both directions	Due to the rhythmic alternating contraction of agonist and antagonist muscles
Paroxysmal dyskinesia	Combination of several hyperkinetic, chorea, athetosis, ballism, and dystonic postures disorders, which occur uni- or bilaterally, affecting multiple body segments	Duration between minutes and hours They can be induced by movements (e.g. paroxysmal kinesigenic dyskinesia) or from coffee/alcohol intake or sleep deprivation (paroxysmal non-kinesigenic dyskinesia) The patient may fall and not be able to talk The consciousness is intact

Even patients with Parkinson's disease in the mid-advanced phase may present with the onset of acute severe dyskinetic symptoms in association with hyperpyrexia to configure the dyskinesia-hyperpyrexia syndrome (DHS) [22]. The main risk factors for the development of DHS are an high daily dopaminergic dose, the presence of concomitant infections, and an high environmental temperature [23]. The onset of a DHS may constitute a medical emergency requiring timely treatment with rehydration, antipyretic measures, and circulatory support, along with a reduction in antiparkinsonian drugs.

Mimics

- **Epileptic seizures** with focal motor phenomenology, in which involuntary movements manifest in the form of rhythmic/pseudo-rhythmic myoclonus, unilaterally affecting a body segment. In crises originating from the primary motor area, clonic jerks typically affect several body segments in the distal-proximal direction, according to the so-called Jacksonian

Figure 14.8 **Hyperkinetic disorders**

march [24]. In seizures, the state of consciousness may be altered, while it is preserved in hyperkinetic disorders. However, it should not be overlooked that myoclonic movements can have a critical origin, representing the clinical expression of generalized seizures in patients with specific syndromic pictures [24]. For further information, please refer to Chap. 4.

- **Tetanic syndrome**, the patient usually has spasms that affect specific muscle districts of the head and trunk, associated with pain, intense autonomic reactions, and systemic manifestations, which differentiate the picture from a true hyperkinesia.

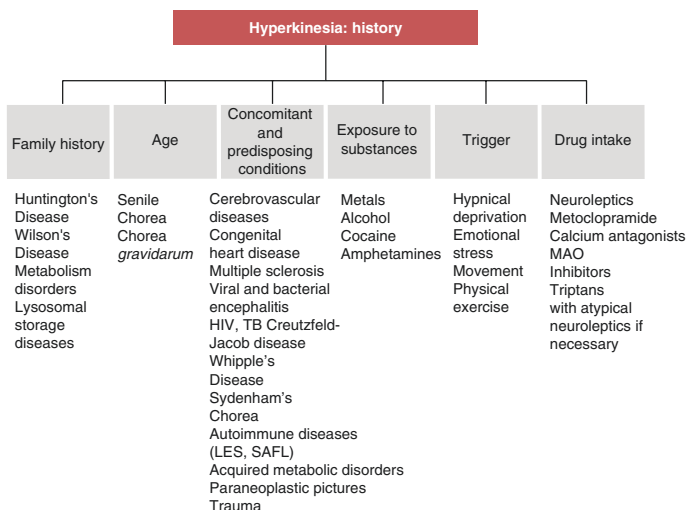
- **Psychogenic disorder**, the patient can simulate tremor or dystonia. These movements generally have an acute onset and an inconsistent, incongruous pattern, which changes rapidly in terms of body distribution and severity. They can regress with distracting manoeuvres and respond to placebo treatments. They are often, but not always, associated with other psychiatric manifestations. For more information, see Chap. 17.

Clinical Evaluation

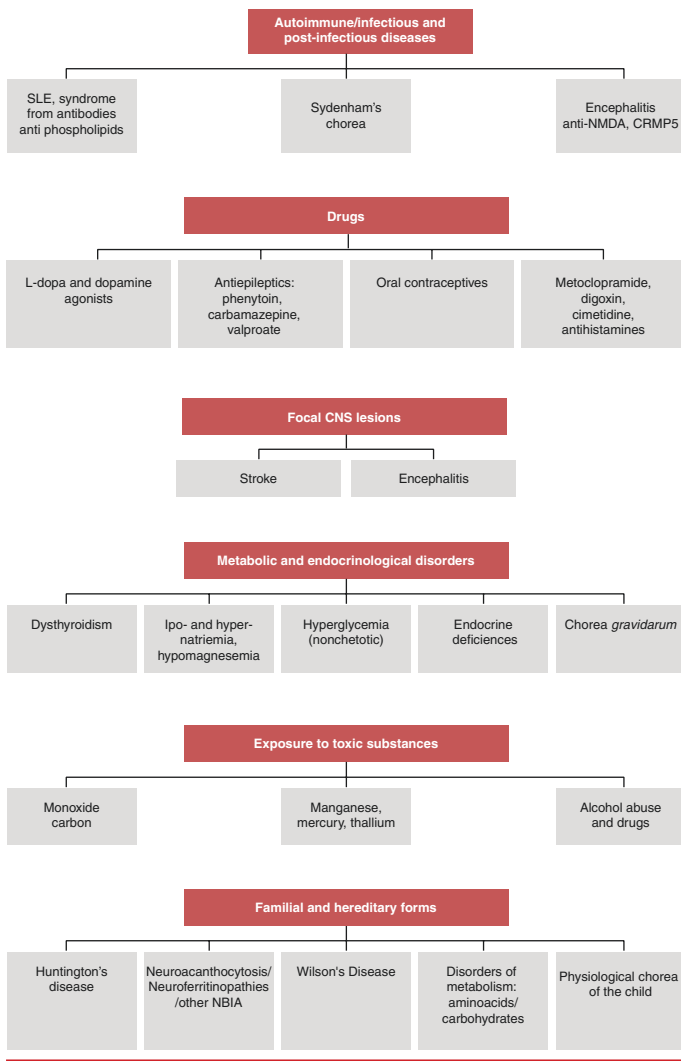
History. Some medical history elements can already be an important aid in the diagnosis (Fig. 14.9):

Family history: Establishing the presence of a family member with a hyperkinetic syndrome is important, as this could represent the first manifestation of a hereditary disease. Chorea, for example, can occur in familiar forms, in not only Huntington's disease and neuroacanthocytosis but also in benign, hereditary variants, beginning in childhood. At the same time, other genetically determined diseases, from metabolic disorders to lysosomal storage diseases and to Wilson's disease, can manifest themselves with various hyperkinetic disorders.

Figure 14.9 **Hyperkinesias: clinical overview**

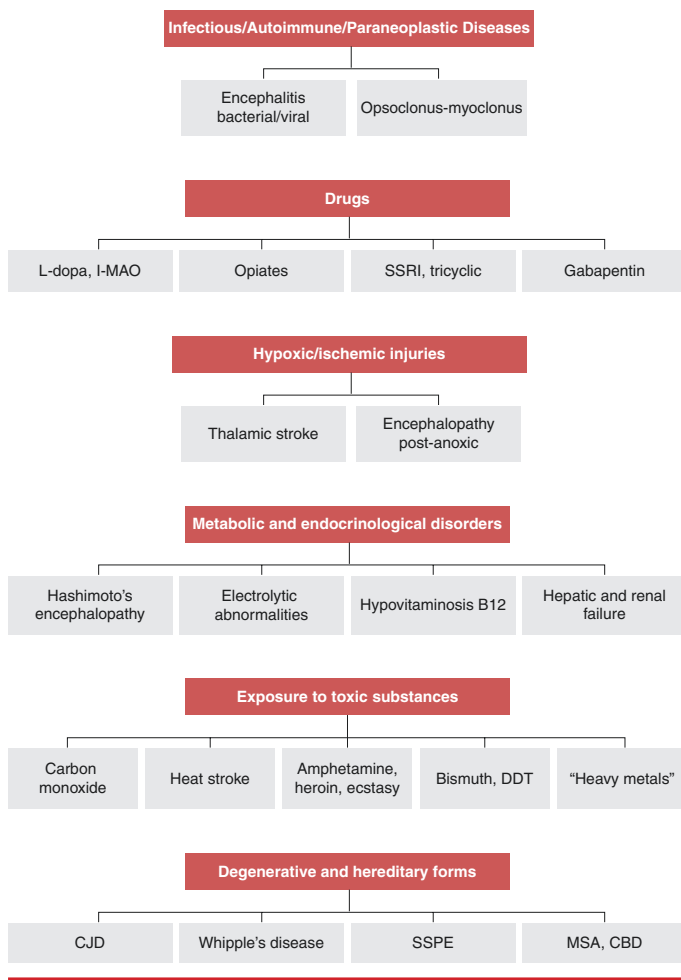


- **Age:** the onset of some clinical pictures may be characteristic in some age groups. Hereditary benign chorea, for example, can occur after the age of 60 in patients without family history or other associated neurological manifestations.
- **Sex:** the sex and the physiological state of the subject under examination can help in the diagnosis. Chorea *gravidarum* usually occurs in the first trimester and resolves in the third, or immediately after the delivery. Hormonal changes can cause the development of chorea patterns, which should be promptly diagnosed and treated, with hydration, rest, and correction of any predisposing conditions [25]. For more information, see Chap. 16.
- **Concomitant and predisposing pathologies:** an acute hyperkinetic disorder can be the manifestation of more complex patterns of central nervous system impairment or systemic disorders:
 - Stroke: in 1–4% of *stroke* patients can be associated pictures characterized by hyperkinesia, usually chorea, ballism, and dystonia [26]. The disorder may occur in the acute phase, at the onset, or after a few months. In most cases, the side of the body contralateral to the lesion is involved (Fig. 14.10); this is generally localized in the basal ganglia typically in the caudate in haemichorea and in the subthalamic nucleus of Luys in haemiballism. However, even a thalamic or cerebellar damage can cause a hyperkinetic movement disorder, and in the latter location, this is homolateral to the lesion [27]. The most common cause is ischemic stroke, secondary to small vessel disease [8].
 - Encephalitis: acute-onset hyperkinesia may also be part of the clinical picture of bacterial, viral, and/or autoimmune forms of encephalitis. In addition, cases of choreic disease associated with tuberculosis meningitis and HIV infection have been described [28, 29]. Myoclonus is more typically associated with rare forms of subacute encephalitis, such as progressive sclerosing panencephalitis, Creutzfeldt-Jakob disease and Whipple's disease, the latter with ocular-facial myorhythmia; in cases with subacute onset, followed by catatonic status and myoclonic jerks with buccal dyskinesia, NMDA encephalitis should always be suspected [30].

Figure 14.10 **Acute-onset chorea**

However, the most frequent form of chorea associated with an infectious agent is Sydenham's chorea, which occurs 1–6 months after an acute beta-haemolytic group A streptococcus infection. Here, chorea is generally bilateral, with asymmetrical distribution and with involvement of the muscles of the tongue, chewing and phonation, resulting in disorders of verbal expression. Behavioural disturbances and an affective illness are frequently associated [31]. For further information, see Chap. 6.

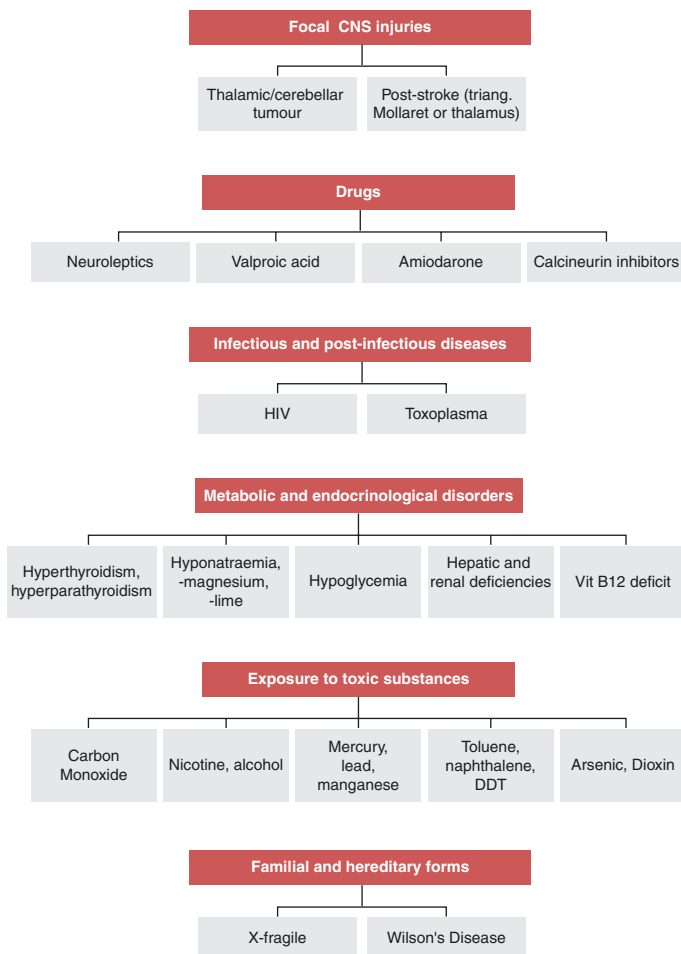
- Autoimmune diseases: chorea is one of the hyperkinetic disorders most frequently associated with autoimmune diseases, from SLE to antiphospholipid antibody syndrome and other autoimmune encephalopathies. In this context, chorea may manifest in the early stage of the illness or may be delayed and induced by the intake of oral contraceptives and by pregnancy [32].
- Metabolic disorders: myoclonus and ballism are the most common. The second most frequent cause of haemiballism is, indeed, a severe non-ketonic hyperglycaemia, more common in women and which may be the initial manifestation of diabetes mellitus [33]. Myoclonus may occur in association with renal and hepatic insufficiency and as a result of cerebral anoxia (Fig. 14.11), secondary to cardiac arrest or acute respiratory insufficiency [33]. In the acute phase after anoxic injury, it is possible to observe a state of myoclonic disease, which can last for hours or days. Lance-Adams syndrome (LAS) is a rare complication of successful cardiopulmonary resuscitation and is often accompanied by action myoclonus. LAS is seen in patients who have undergone a cardiorespiratory arrest, later regained consciousness, and then developed myoclonus days or weeks after the event [34].
- Epilepsy: myoclonus, usually multifocal, can be the manifestation of an epileptic seizure in the context of known group syndromes, such as generalized idiopathic epilepsy and progressive myoclonic epilepsy [35].

Figure 14.11 **Myoclonus in acute cases**

- Paraneoplastic syndromes: hyperkinetic disorders, such as opsoclonus-myoclonus syndrome, characterized by arrhythmic, continuous, multidirectional saccadic movements, and by myoclonus of the trunk and limbs, may occur in adults with lung cancer (mainly microcytoma) and breast cancer,

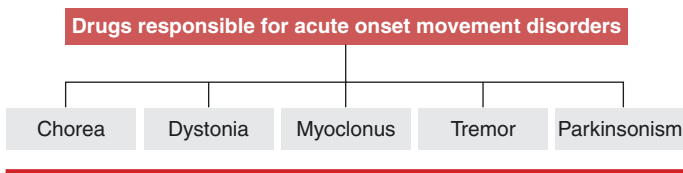
more rarely with other neoplasms, while in children with neuroblastoma [36].

- Other CNS diseases: a hyperkinetic movement disorder can also worsen the course of CNS diseases, such as multiple sclerosis (so-called tonic spasms) and head trauma.
- Retropharyngeal abscess, tumour in the posterior cranial fossa, or cervical spine: an acute, 'torticollis-like' dystonia, at sudden onset in paediatric age, can be the complication of a tonsillitis and, therefore, of a retropharyngeal abscess or of a cancer in posterior cranial fossa or of the cervical spine [37, 38].
- Exposure to toxic substances: when collecting the medical history, exposure to environmental toxins, such as carbon monoxide and metals (mercury, manganese, thallium), and the intake of abuse substances, such as alcohol, cocaine, and amphetamines, which can often lead to symptomatic tremor, should be considered (Fig. 14.12).
- Drugs: a careful examination of the patient's therapy can be decisive at the diagnostic level, as many pharmacological classes can induce hyperkinetic disorders (Fig. 14.13). Chorea can be triggered by neuroleptics, antiepileptic, steroids, oral contraceptives, opioids, and tricyclic antidepressants. Myoclonus may occur following the intake of selective serotonin reuptake inhibitors, MAO inhibitors, and triptans. However, the most common disorder associated with drugs is acute dystonia. This is a condition commonly seen in the emergency room, induced by drugs that cause a blockage of the striatal dopaminergic receptors D2 [20]. Antipsychotics are among the drugs most commonly inducing this reaction, particularly typical neuroleptics such as haloperidol and fluphenazine. Dystonia generally occurs within a few days after the initiation of treatment or a dose increase [39]. Young age, female gender, cocaine abuse, and a positive history of previous dystonia are risk factors [39]. Metoclopramide, a commonly used antiemetic, can also trigger an acute dystonic reaction in 0.2–1% of subjects taking it, most frequently in juvenile and female sex [40]. Other categories of drugs may also be involved, including calcium channel blockers (cinnarizine, flunarizine), antiepileptic (carbamazepine, phenytoin), antimalarial, and abuse

Figure 14.12 **Acute tremor**

substances, such as cocaine and 3,4-methylenedioxyamphetamine [39]. Medication-induced acute dystonia generally affects head and neck muscles (stiff neck, trismus, forced mouth opening, blepharospasm). More rarely, hand muscles may be affected. Sometimes, dystonia is only visi-

Figure 14.13 Drugs and movement disorders of acute onset



ble after muscle activation (action-dystonia). Characteristic are the oculogyric crises, in which the patient presents a forced deviation of the gaze, mainly upwards, lasting even hours [40]. The so-called Gerhardt syndrome may also be the manifestation of a drug-induced acute laryngeal dystonia in which the vocal cords undergo an adduction spasm during inhalation, causing a severe stridor and a respiratory impairment [41].

Neurological Examination

The neurological examination of a patient with acute-onset hyperkinetic disorder is aimed at identifying the clinical characteristics of the movement and the association of any alterations of the remaining neurological examination.

■ Phenomenological features of the movement:

- **Velocity:** a rapid and short movement is typical of chorea, myoclonus, and ballism; in the latter case, the movement can be sometimes violent. A slower movement characterizes dystonia and athetosis. Tremor can be rapid or slow, depending on the frequency of the movement.
- **Rhythmicity:** tremor is the only involuntary movement characterized by a rhythmicity; all other hyperkinetic disorders are irregular.
- **Distribution:** all muscle segments, from facial to limb segments, can be involved in chorea, dystonia, and tremor. Ballism typically affects the proximal muscles of the limbs, while athetosis is the most distal. Myoclonus can be focal, affecting only certain muscle groups, or generalized involving the trunk. Axial myoclonus, for example, is characterized by a flexion contraction of the trunk and neck, with abduction of the limbs and flexion of the hips. Axial myoc-

lonus involves the paravertebral musculature, causing flexion movements of the trunk. As far as the affected side of the soma is concerned, disorders such as chorea, dystonia, athetosis, and myoclonus can have a bilateral, sometimes asymmetrical, manifestation. Tremor and ballism can often only affect one body side.

- Triggering factors:
 - Some voluntary gestures or actions may trigger a hyperkinetic disorder. Dystonia, for example, is typically elicited by the execution of specific motor tasks. Other disorders, such as myoclonus, can be triggered by sensory stimuli.
- Response to manoeuvres:
 - Some manoeuvres can help the improvement of the disorder as a 'geste antagoniste' in a dystonia. On the other hand, a psychogenic hyperkinetic disorder can be resolved or modified in its pattern by having the patient perform cognitive or motor *distracting* manoeuvres (Table 14.4).
- Other neurological signs:
 - The detection of other neurological signs, in addition to the hyperkinetic phenomena, can be useful both for the differential diagnosis (e.g. an impairment in the state of consciousness could suggest a critical phenomenon rather than a disorder of movement) and for the definition of the underlying aetiopathogenetic mechanism.

Table 14.4 Specific clinical aspects of psychogenic hyperkinetic disorders

Patterns not consistent with a disorder on an organic basis:

- Fixed dystonia
 - Unusual distribution: onset in the lower limbs in adulthood, haemifacial dystonia
 - Inconsistent activation patterns
 - *Facies martyrea*
-

Distraction effect, persistent placebo effect

Absence of other organic signs

Extreme generalized slowness, bizarre postures

Positive history of psychiatric disorder

Diagnostic Procedures

Although clinical evaluation (history and neurological examination) is the cornerstone of the diagnostic approach to a hyperkinetic movement disorder, it may be necessary to perform confirmative instrumental and laboratory tests.

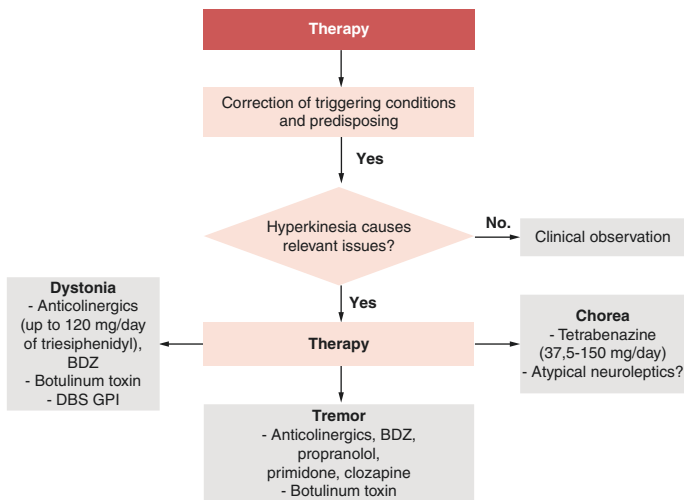
A patient with additional neurological signs than hyperkinesia, localized in a hemi-body, and a negative medical history of exposure to toxic substances medication should undergo an emergency brain scan.

As far as laboratory tests are concerned, it could be useful to perform blood count, liver and kidney function, electrolytes, and TSH. In some cases where an exposure to toxic substances is suspected, a haemodialysis and toxicological examination should also be considered. In the case of suspicion of tetanic contraction, an EMG test is essential for diagnostic confirmation.

Treatment

A patient with an acute-onset hyperkinetic disorder, assessed in the emergency room, should be admitted when an underlying central or systemic nervous system disorder is suspected and requires prompt therapeutic intervention. In other cases, when the therapy administered does not lead to a rapid resolution of the picture, a period of (brief) clinical observation may be recommended.

The therapy of acute hyperkinetic disorders is mainly aimed at correcting the triggering and predisposing conditions. In specific cases and when the intensity of the symptoms is severe, such as in acute dystonia, anticholinergics can be recommended, while in Huntington's chorea tetrabenazine, which is a presynaptic dopamine depletor, can be successfully used (Fig. 14.14). Acute forms of haemiballism are often self-limiting and generally do not require symptomatic treatment. In tardive hyperkinetic forms related to the use of typical neuroleptics, an attempt to switch to atypical neuroleptics is warranted. The onset of a dyskinetic crisis in a patient with Parkinson's disease may represent a medical emergency requiring a swift reduction in antiparkinson drugs associated with rehydration and circulatory support.

Figure 14.14 **Hyperkinetic disorders: therapeutic approach**

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15.

Respiratory Emergencies in Neurological Diseases

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Introduction

Many neurological diseases can cause acute respiratory failure (ARF) due to impairment of bulbar respiratory control centres, cervical or thoracic spinal cord, motor neurons, peripheral nerves, neuromuscular junction, or skeletal muscles. **Hypoxemia and/or hypercapnia** can be a complication of cerebrovascular diseases, brain tumours, head or spinal trauma, and infectious, inflammatory, or degenerative diseases of the central nervous system, by their direct effect or the onset of complications such as bronchopneumonia, pulmonary oedema, or traumatic pneumothorax [1].

Respiratory failure (RF) can often also occur in patients with acute or chronic neuromuscular diseases such as Guillain-Barré syndrome (GBS), amyotrophic lateral sclerosis (ALS), myasthenia gravis (MG), spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), polymyositis, or dermatomyositis. In these cases, weakness of the diaphragm and intercostal muscles, or concomitant respiratory complications, due to oropharyngeal dysfunction with aspiration of secretions, food and/or fluids associated with an inefficient cough may lead to respiratory emergencies [2]. In all these conditions, respiratory impairment increases the burden of pre-existing disease and its mortality rate.

Acute respiratory emergencies may occur in neurological diseases at the onset or more often during their chronic course and in this case at home, following direct access to the emergency room (ER) or during hospitalization for follow-up checks. In addition, the longer survival of patients with genetic neuromuscular diseases such as SMA and DMD has increased the need to address the problems of transition from paediatric to adult health care, with repercussions even for what regards respiratory emergencies [3, 4].

Pathogenesis of ARF

RF is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide (CO₂) elimination. According to pathogenetic mechanism, RF can be distinguished into two different types:

- **Type 1 or hypoxemic RF**, which is characterized by a reduced oxygen supply (also referred to as *lung failure*)
- **Type 2 or hypercapnic RF**, which is characterized by abnormal retention of CO₂ (also referred to as *pump failure*)

In subjects with neurological disorders, the onset of ARF is primarily attributable to pump failure: in such a condition, ventilatory pump, i.e. the total anatomical and functional apparatus which allows normal ventilation of the lungs, including the structures ranging from the cerebral cortex to the respiratory muscles, fails to provide an adequate alveolar ventilation [5].

Pump failure can be attributed to an imbalance between the reduced capacity of the inspiratory muscles and the increased mechanical load on the respiratory muscles: this condition is the prerequisite for the occurrence of respiratory muscle fatigue, which in turn leads to a reduction in lung ventilation and CO₂ retention. Indeed, the adaptive response of respiratory muscles to the occurrence of muscle fatigue consists in reducing the amount of muscle effort. Actually, the respiratory control centres reset the breathing pattern by shortening the duration of the inspiratory phase (Ti) and reducing the value of Ti/Ttot ratio (i.e. the ratio between the duration of the inspiratory phase and the total duration of the respiratory cycle). The modified breathing pattern necessarily leads to a reduction in alveolar ventilation, as shortening of inspiratory time causes a reduction in tidal volume, i.e. the amount of air ventilated to the lung during a single breath.

Respiratory muscle weakness, resulting in a reduced capacity of generating pressure, increases the ratio between negative pleural pressure during quiet breathing and maximal negative pleural pressure, predisposing to the occurrence of respiratory muscle fatigue and failure. Accordingly, it has been reported that the amount of CO₂ retention directly correlates with the severity of respiratory muscle weakness, as assessed by the measure of maximal inspiratory pressure (MIP) at the mouth [6, 7]. This relationship has been demonstrated in patients with acute poliomyelitis and/or **complete traumatic sections of the cervical spinal cord**, C1–C3, resulting in a partial or total de-recruitment of the diaphragmatic muscle fibres. In this event, RF may become irreversible or result in

a partial recovery of ventilatory function which can be maintained even for several years [8].

In patients with **Duchenne muscular dystrophy**, ARF may exacerbate a **pre-existing chronic respiratory failure** (CRF), which can be worsened by precipitating factors including pneumonia, otherwise benign upper respiratory tract infection, and congestive heart failure, as well as **incongruous oxygen therapy** or a state of severe malnutrition.

The verification of hypercapnia due to pump failure necessarily indicates the application of ventilatory assistance.

Lung failure may result from respiratory tract infection with bronchial mucous encumbrance and/or an inhalation episode, leading to the development of atelectasis or dystelectasis. In both cases, an alteration of ventilation/perfusion ratio (V/Q ratio) may occur: indeed, regional ventilation is reduced, in relation to blood flow, to the point that alveolar PO_2 (PaO_2) decreases and arterial blood from the hypoventilated lung zones shows a reduced oxyhaemoglobin saturation. Hypoxemia due to V/Q mismatching can be corrected by a limited increase in O_2 inspiratory fraction obtained by **the administration of supplementary oxygen**: however, this therapeutic strategy should be used with great caution and requires careful patient monitoring, as it can induce a depression of ventilatory drive and acute CO_2 retention.

Impairment of the autonomic nervous system may contribute to the onset of respiratory complications in various conditions including stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, tetanus, botulism, and GBS. An important role is played by a sympathetic storm with reduction in vagal tone, decreased bronchodilator effect of anticholinergic drugs, and reduced ventilatory response to hypoxia and hypercapnia probably caused by a disrupted transmission of aortic and carotid sinus mechanoreceptors [9].

Pathogenesis of Respiratory Complications

Table 15.1 lists the neurological diseases most frequently associated with the onset of ARF.

Table 15.1 Neurological diseases and pathogenic mechanisms causing respiratory complications

Disease	Pathogenic mechanisms	Respiratory complications
Stroke [10–13]	<ul style="list-style-type: none"> • Altered breathing control • Reduction of maximum voluntary strength and endurance of inspiratory and expiratory muscles • Poorly efficient thoracic wall mechanics • Altered vigilance • Inefficient coughing 	<ul style="list-style-type: none"> • Ataxic or cluster breathing • Cheyne-Stokes breathing • Pulmonary infections (frequent in 1/3) with the risk of death up to three times greater in the first 30 days, lengthening of hospital stay and the presence of more serious outcomes at discharge
Convulsive status epilepticus [14]	<ul style="list-style-type: none"> • Status epilepticus • Drugs used 	<ul style="list-style-type: none"> • ARF frequency: about 80% • Aspiration pneumonia • Pulmonary oedema
Head trauma [15, 16]	<ul style="list-style-type: none"> • Loss of pharyngeal muscle tone • Loss of swallowing and coughing reflexes • Compromised respiratory control 	<ul style="list-style-type: none"> • ARF: hypoxemic and hypercapnic
Spinal cord injury [17–19]	<ul style="list-style-type: none"> • Diaphragm paralysis (C3–C5 injury) • Paralysis of intercostal muscles used for inspiration (T1–T12 injury) • Paralysis of intercostal and abdominal muscles used for expiration (T5–T12 injury) • Poor cough efficiency • Increased bronchial secretions and bronchospasm (vagal hypertonia due to sympathetic damage at C8–L2 level) 	<ul style="list-style-type: none"> • Possible worsening in the first 5 days with need for intubation • In 67% of cervical lesions, the onset of atelectasis (36%), pneumonia (31%), respiratory failure (23%) • Pulmonary oedema • Pneumothorax

Continued

Table 15.1 Continued

Disease	Pathogenic mechanisms	Respiratory complications
Multiple sclerosis [20]	<ul style="list-style-type: none"> • Bulbar dysfunction with dysphagia • Altered central breathing control • Breathing disturbances during sleep 	<ul style="list-style-type: none"> • Neurogenic pulmonary oedema • Sepsis • ARF
Encephalitis [21]	<ul style="list-style-type: none"> • Poor vomiting reflex • Accumulation of secretions • Dysphagia 	<ul style="list-style-type: none"> • Aspiration pneumonia • Respiratory failure
Parkinson's disease [22–25]	<ul style="list-style-type: none"> • Reduced thoracic wall compliance due to severe rigidity • Hypokinesia and upper airway dyskinesia • Swallowing disturbances • Weak cough • Upper airway obstruction (UAO) 	<ul style="list-style-type: none"> • Dyspnoea and chest pain • Respiratory stridor due to UAO • Restrictive respiratory dysfunction • Aspiration pneumonia
Ataxia [26–28]	<ul style="list-style-type: none"> • Reduced airway clearance • Weak cough • Dysphagia • Upper airway obstruction 	<ul style="list-style-type: none"> • Restrictive respiratory dysfunction • Aspiration pneumonia
Tetanus and botulism [29]	<ul style="list-style-type: none"> • Rapid worsening if not treated with Ig and assisted in intensive care unit (ICU) 	<ul style="list-style-type: none"> • Respiratory failure in 100%
Neuromuscular diseases [3, 30–33]	<ul style="list-style-type: none"> • Weakness of the diaphragm, intercostal, pectoral, scalene, sternocleidomastoid muscles • Possible presence of scoliosis • Swallowing disorder • Inefficient coughing 	<ul style="list-style-type: none"> • Restrictive respiratory failure • Aspiration pneumonia

Table 15.2 shows the neuromuscular diseases that develop chronic progressive respiratory failure in adolescence or adulthood. If you are working at ER or any emergency setting, and you meet a patient with hypercapnic RF, you should always try to collect detailed information about the type of disease already diagnosed or suspected, as the prognosis and treatment can be very different.

Table 15.2 Neuromuscular diseases with chronic progressive respiratory failure

Inevitable

Spinal muscular atrophy type 1
Duchenne muscular dystrophy (DMD)
Amyotrophic lateral sclerosis (ALS)
Some limb-girdle muscular dystrophies with juvenile onset (e.g. sarcoglycanopathies)
Some Hereditary myopathy with early respiratory failure

Frequent

Spinal muscular atrophy type 2
Myotonic dystrophy type 1 (DM1)
Late-onset Pompe disease (LOPD)
Guillain-Barré syndrome (GBS—acute demyelinating polyneuropathy)
Myasthenia gravis (MG)
Facioscapulohumeral muscular dystrophy (FSHD)
Congenital muscular dystrophies (e.g. Ullrich CMD)
Limb-girdle muscular dystrophies (e.g. calpainopathy, FKRP)
Some congenital myopathies (e.g. centronuclear myopathy)
Congenital myasthenic syndromes

Occasional

Becker muscular dystrophy (BMD)
Hereditary polyneuropathies (CMT1B, 4)
Inflammatory myopathies
Spinal muscular atrophy type 3
Some congenital myopathies
Mitochondrial myopathies

Rare

Ocular-pharyngeal muscular dystrophy
Charcot-Marie-Tooth disease (CMT)
CIDP (chronic inflammatory demyelinating polyneuropathy)

Table 15.3 Adult neuromuscular diseases that may present with acute respiratory failure

-
- Myasthenia gravis
 - ALS
 - Pompe disease
 - Myotonic dystrophy type 1
 - Myofibrillary myopathies
 - Other rare (e.g. limb-girdle muscular dystrophy type 2I)
-

In addition, since **some patients with neuromuscular disease may develop acute or subacute respiratory failure at the onset**, before presenting with obvious motor signs (e.g. walking patients with Pompe disease without a diagnosis yet), a differential diagnosis should be made to identify forms that may benefit from specific treatment (Table 15.3).

Clinical Management and Treatment

Acute Respiratory Failure in Chronic Progressive Neurological Diseases (Acute on Chronic Respiratory Failure)

Movement Disorders

Most patients with **Parkinson's disease**, who develop ARF requiring ventilatory assistance, need tracheal intubation in order to protect the airways from the risk of inhalation. At ER admission, patients not rarely present with laryngeal stridor due to paralysis of the vocal cords and laryngeal dystonia; in this situation, intubation becomes difficult and requires bronchoscopy assistance [34]. Weaning from mechanical ventilation can be prolonged due to the occurrence of respiratory complications (i.e. ventilator-associated pneumonia) [35]. In some cases, the recurrence of laryngeal stridor indicates the need for tracheostomy.

Sporadic cases of **myoclonus** associated with progressive encephalomyelitis have been reported as possible causes of ARF, due to impairment in ventilation and swallowing. They may require tracheal intubation and invasive mechanical ventilation (IMV) [36].

In patients with **Huntington's disease**, aspiration pneumonia is the leading cause of death (in about 70% of cases) and is commonly associated with severe dysphagia. For this reason, in the event of ARF, it is essential to administer IMV, in order to protect the airways [37].

Chronic Neuromuscular Diseases with Slow Progression

- Slowly progressive neuromuscular diseases that most frequently present respiratory problems are DMD, SMA, ALS, and myotonic dystrophy type 1 (DM1).
- The main mechanisms underlying respiratory problems are as follows:
 - The **weakness of the inspiratory muscles**, which results in alveolar hypoventilation and hypercapnic CRF, initially only at night and later, as the disease progresses, even during all the day.
 - The **weakness of the expiratory muscles** that causes, especially when associated with weakness of the inspiratory muscles, inefficient cough with accumulation of bronchial secretions and high risk of airway infections [38–40]. The risk of developing CRF further increases if a severe dysfunction of the bulbar muscles is associated, leading to dysphagia and inhalation risk (more frequent in SMA and ALS). The presence of severe scoliosis, which develops mainly in neuromuscular diseases leading to loss of gait before adulthood, is another important risk factor for the development of CRF [41]. All neuromuscular patients with a forced vital capacity (FVC) of less than 50% of the predicted value are at risk of developing nocturnal CRF and poor cough efficiency [42].
- In patients already complicated by CRF, an acute intercurrent event, even of minor degree, can lead to an exacerbation of CRF (Table 15.4). However, it is possible that these patients may be complicated by ARF, even before they have developed a CRF, especially if they have a forced vital capacity of less than 50% of the predicted value. **Infections of the upper and lower airways are the most frequent causes of ARF.**
- Respiratory infections cause an increase in bronchial secretions that, in the presence of poor cough, lead to the encumbrance of the airways and the formation of mucus plugs, which determine hypox-

Table 15.4 Causes of acute respiratory failure in patients with slowly progressive neuromuscular diseases

Most common causes	Upper airway infections (flu, parainfluenza syndrome, acute bacterial bronchitis)
Frequent causes	Community pneumonia (in home patients) Pneumonia related to care practices (in long-term care facilities) Inhalation pneumonia (to be considered especially in the presence of severe dysphagia) Atelectasis
Rare causes	Cardiogenic pulmonary oedema (in patients with associated cardiomyopathy) Pneumothorax Adipose embolism (to be considered in patients complicated by bone fracture) Drug overdose (drugs reducing muscle strength or respiratory drive such as benzodiazepines, opioids, anaesthetics, etc.) Pulmonary embolism Tracheoesophageal and tracheoarterial fistula (in tracheotomized patients) Severe gastric and/or colonic distension

emia by alteration of ventilation/perfusion ratio and increased muscle work. Increased respiratory work overloads the inspiratory muscles already weakened by existing neurological disease, leading to acute hypercapnia or aggravating chronic hypercapnia.

- The use of **non-invasive ventilation** (NIV), **manual cough assistance** (i.e. the use of lung recruitment manoeuvres with an **Ambu bag** associated with the thoraco-abdominal thrust), or **mechanical insufflator-exsufflator** (also known as the cough machine) and the **early use of antibiotics** are the standard of care in the event of airway infection, both at home [43–47] and in hospital [39, 48–51].
- Respiratory exacerbations of infectious origin can be managed at home if the patient and his/her family members have been trained in the use of home ARF management protocols, which include the use of NIV, cough care, pulsatile oximetry monitoring, and early use of antibiotics. These protocols must also clearly define when to admit the patient to hospital, must be adapted to the local organizational reality, and must include the involvement of a doctor who visits the patient at home.

Patients with a forced vital capacity of less than 50% of the predicted value or who have had frequent hospital admissions due to respiratory exacerbation in the last year may be considered eligible for such protocols. **If home treatment fails, the patient must be hospitalized** in a ward where a doctor is present 24 h/day and where devices and number of nurses are appropriate to ensure adequate monitoring of vital parameters.

- If the patient has a $\text{SaO}_2 < 95\%$ or has decompensated hypercapnia ($\text{pH} < 7.35$ with $\text{PCO}_2 > 45$ mmHg), he/she should be ventilated, preferably in a non-invasive manner and, in the presence of an increase in bronchial secretions, should be promptly treated with manual or mechanical coughing assistance [48–50]. If instead there is at least one **criterion that contraindicates the NIV** (Table 15.5), tracheal intubation must be considered immediately.
- **O_2 should never be used unless associated with the use of non-invasive ventilation and CO_2 monitoring.**
- A chest X-ray should be performed as soon as possible to assess the **presence of pneumonia or atelectasis**. Furthermore, if there is no clear infectious cause, noninfectious causes of ARF (pneumothorax, pulmonary thromboembolism, adipose embolism) should be excluded. In patients with **myopathy complicated by cardiomyopathy** (Table 15.6), an echocardiogram should also be performed in order to rule out the possibility of cardiogenic pulmonary oedema. If the chest X-ray does not justify the clinical picture of the ARF, a chest CT scan is required to exclude an **anterior pneumothorax that is not visible on the chest X-ray**. If even chest CT scan does not show any cause for ARF, it is useful to administer contrast medium to **exclude a pulmonary thromboembolism**.
- The effectiveness of NIV and manual or mechanical cough assistance should be assessed by arterial blood gas (ABG) analysis

Table 15.5 Contraindications to non-invasive ventilation

-
- Unconscious or uncooperative patient
 - Psychomotor agitation
 - Severe difficulty in swallowing
 - Bronchial secretions not managed by coughing techniques
 - Severe hypoxemia ($\text{PaO}_2 < 60$ mmHg with $\text{FiO}_2 > 0.6$)
 - Undrained pneumothorax
 - Coexistence of two other organ failures
-

Table 15.6 Neuromuscular diseases complicated by cardiomyopathy

Disease	Cardiac complications
Dystrophinopathies (DMD, BMD)	Dilated cardiomyopathy (more frequent), conduction disorders, and arrhythmias
Limb-girdle muscular dystrophies (rarely)	Conduction disorders and arrhythmias (more frequent), dilated cardiomyopathy
Myotonic dystrophies	
Emery-Dreifuss muscular dystrophy	
Myofibrillary myopathies	Conduction disorders and arrhythmias (more frequent), hypertrophic cardiomyopathy, noncompacted myocardium, dilated cardiomyopathy
Mitochondrial myopathies	
Pompe disease (glycogenosis type II)	Hypertrophic cardiomyopathy in the infantile form
Lipid storage myopathies	Dilated cardiomyopathy, hypertrophic cardiomyopathy

within 1–2 h after the start of NIV. If severe decompensated respiratory acidosis or clinical signs of severe respiratory decompensation persist (persistence of dyspnoea, high heart rate and/or respiratory rate, use of respiratory accessory muscles, poor expansion of the ribcage), the failure of the NIV should be considered.

- If **family members or caregivers are trained in ventilator use** and cough care, their continued presence at the patient's bedside throughout hospitalization is critical to the success of the non-invasive approach.
- If non-invasive treatment (NIV and coughing assistance) fails, **tracheal intubation** is necessary. In such cases, a possible difficult airway management must be carefully assessed. In this case, it is important to proceed with intubation under conditions of relative control of oxygenation, avoiding to intubate the patient in the presence of a severe hypoxemia, and preferably under bronchoscopic guidance.
- As soon as the acute process leading to tracheal intubation is in resolution, the patient can be **weaned by the ventilator**, reducing FiO_2 (percentage of inhaled O_2) and using the cough machine to resolve the desaturations caused by encumbrance of the airways by bronchial secretions. Immediately after extubation, the NIV associated with the use of the coughing

Table 15.7 Intervention strategies in patients with chronic progressive neurological disease and “acute on chronic” RF

Disease	Clinical signs	Procedures
Parkinson's disease	<ul style="list-style-type: none"> • Laryngeal stridor • Vocal cord paralysis • Laryngeal dystonia 	<ul style="list-style-type: none"> • Consider tracheal intubation or palliative care • For subsequent weaning, attention to respiratory complications • If symptoms and signs persist, tracheostomy is indicated
Huntington's disease	<ul style="list-style-type: none"> • Dysphagia • Aspiration pneumonia 	<ul style="list-style-type: none"> • Tracheal intubation
DMD SMA ALS DM1 Other neuromuscular diseases	<ul style="list-style-type: none"> • If coughing inefficient, in case of infections of the upper or lower airways, risk of retained bronchial secretions • If dysphagia, risk of aspiration pneumonia • If forced vital capacity <50%, the risk of ARF increases • ARF if SaO₂ <95% and/or pH <7.35 with PCO₂ >45 mmHg associated with any of the following: <ul style="list-style-type: none"> – Accumulation of bronchial secretions – Dyspnoea – High heart and/or respiratory rate 	<ul style="list-style-type: none"> • NIV and ABG analysis within 1–2 h • Manual cough assistance (Ambu bag, cough machine) • Pulse oximeter monitoring • Early use of antibiotics • If NIV is contraindicated (Table 15.5), tracheal intubation • Never use O₂ unless associated with NIV and CO₂ monitoring • Echocardiogram to exclude cardiogenic pulmonary oedema • Chest CT scan (pneumothorax not visible on X-Ray or pulmonary embolism?) • If ineffective NIV, tracheal intubation

machine must be applied [52, 53]. Tracheostomy can be considered after multiple unsuccessful weaning trials.

Table 15.7 summarizes the clinical signs and procedures to be implemented in **patients with chronic neurological disease and ARF**.

Rapidly Progressive Acute Respiratory Failure

Stroke

Treatment of stroke-related ARF often requires administration of **tracheal intubation and IMV**. In fact, impaired control of ventilation due to brain damage is frequently associated to loss of pharyngeal muscle tone, cough reflex, and swallowing, conditions that compromise the ability to protect the airways and increase the risk of inhalation [54]. The latter may be aggravated by a concomitant altered state of consciousness. Other complications can compromise respiratory function, including pneumonia, pulmonary embolism, and pulmonary oedema. For this reason, stroke patients who develop ARF require close cardio-respiratory monitoring to detect sudden changes in clinical conditions at an early stage.

Mortality rate of patients who need to be intubated is high: only 50% survive at 30 days and 30% at 1 year [55].

Predictors of an increased risk of mortality include a low score of Glasgow Coma Scale and lack of pupil reflex at the time of intubation. Surviving patients usually recover with a good functional autonomy and the ability to regularly perform activities of daily living in two-thirds of cases. Intubated patients present a high risk of pneumonia caused by colonization of the oropharynx or contamination by equipment and/or care staff.

Convulsive Status Epilepticus

Oro-tracheal intubation and mechanical ventilation allow to maintain normal capnia and oxygenation and to use intravenous anaesthetics to treat epilepsy. Moreover, they prevent lung inhalation [14].

The delay of intubation is associated with increased mortality [56]. Therefore, endotracheal intubation can only be avoided if the recovery of consciousness is rapid.

Severe Head Injury

In severe head trauma (Glasgow Coma Scale below 9), in order to reduce morbidity and mortality, it is a priority to avoid **secondary brain damage that is caused not only by arterial**

hypotension and endocranial hypertension but also by hypoxemia and hypercapnia.

For this purpose, patients must be intubated, and IMV must be set to maintain normal capnia and oxygenation. **Intubation** also allows the patient to be sedated, reducing endocranial pressure and preventing pulmonary inhalation [57].

Spinal Cord Injuries

In patients with a complete lesion above C5, intubation and IMV are always required, while in patients with an incomplete lesion and a lesion below C5, intubation can be avoided. In the latter patients, in order to assess the need for invasive or non-invasive ventilatory care, it is essential to monitor not only pulse oximeter but also CO₂, vital capacity, and MIP [58].

Diaphragmatic Paralysis

- Phrenic nerve neuropathy can lead to diaphragmatic paralysis and respiratory dysfunction of varying degree.
- Monolateral diaphragmatic paralysis is often asymptomatic and is usually suspected in the presence of occasional finding of **elevated hemidiaphragm**. It can cause dyspnoea during effort or in supine position, especially in the presence of a concomitant abdominal distension (obesity or pregnancy) or of a concomitant pulmonary or cardiac pathology [59].
- **Bilateral diaphragmatic paralysis** leads to orthopnoea and chronic nocturnal hypoventilation and can be complicated by hypercapnic ARF. It can be diagnosed in the presence of a 30% drop in vital capacity with the assumption of a supine position [60].

Rapidly Evolving Neuromuscular Diseases

In the event of a **myasthenic crisis**, the onset of ARF secondary to pump failure is a common occurrence, although the values of FVC and maximal mouth pressures may still be adequate in stable clinical conditions. ARF arises from the combination of altered transmission at the level of neuromuscular junction, depression of the respiratory drive, and reduced muscle endurance [5]. **ARF onset can be precipitated by an infection of the respiratory tract, the**

occurrence of glucocorticoid-induced myopathy, the specific involvement of bulbar muscles, or sequelae of the previous thymectomy.

In **Guillain-Barré syndrome**, demyelination of peripheral nerve fibres may alter the conduction of efferent stimuli to the respiratory and bulbar muscles; as a result, 20–30% of patients need ventilatory support [32]. The diaphragm is specifically involved, as documented by the marked decrease in FVC value after the transition from upright to the supine position.

In the event of rapidly evolving neuromuscular diseases, **timely identification of those patients who need ventilatory assistance becomes essential** in order to avoid complications potentially linked to urgent intubation. The need for MV is likely in patients with rapid progression of the disease, bulbar dysfunction (characterized by dysarthria, dysphagia, or ineffective cough), bilateral facial muscle weakness, or dysautonomia. In support of the decision to administer endotracheal intubation, the 20/30/40 rule has been proposed: according to this rule, the procedure is recommended in those patients showing: FVC <20 mL/kg; MIP <−30 cm H₂O; maximal expiratory pressure (MEP) <40 cm H₂O [5]. Other indicators of an urgent need for IMV and airway protection include the inability to lift the head and the rapid development of ARF (within 1 week).

With regard to the modes of ventilatory assistance, it should be noted that, **except for some patients with myasthenic crisis at an early stage, the application of NIV has a very limited role**, due to the inability of eliminating bronchial secretions. On the other hand, once intubated, patients have an increased risk of pulmonary complications, including ventilator-associated pneumonia: its occurrence is associated with older age, low level of serum bicarbonates, and prolonged duration of intubation. Early tracheostomy is recommended whether a prolonged duration of intubation is expected.

Table 15.8 summarizes the clinical signs and procedures to be implemented in patients with ARF in rapidly progressive neurological diseases.

Table 15.8 Intervention strategies in patients with ARF in rapidly progressive neurological diseases

Disease	Clinical signs	Procedures
Stroke	Loss of cough reflex, severe dysphagia, GCS <9 associated with ARF	Consider tracheal intubation and mechanical ventilation or palliative care
Convulsive status epilepticus	If recovery of consciousness is not rapid	Consider tracheal intubation and mechanical ventilation
Severe head injury	If GCS <9	Consider tracheal intubation and mechanical ventilation
Spinal cord injuries	If complete lesion above C5	Tracheal intubation and mechanical ventilation
Critical illness myopathy or polyneuropathy (patient in ICU)	Flaccid paralysis with prolonged dependence on the ventilator	Promote early mobilization, avoid prolonged use of neuromuscular blockers and steroids, avoid prolonged controlled ventilation
Ventilator-induced diaphragmatic dysfunction	Prolonged dependence on the ventilator	Avoid prolonged controlled ventilation; avoid during assisted ventilation: <ul style="list-style-type: none"> – Fan dis-synchronism – Ventilator over- or undersupply
Diaphragmatic paralysis	If the fall in FVC is greater than 30% in a supine position compared to the FVC measured in a seated position	Consider NIV
Myasthenia gravis, GBS	If FVC <20 ml/kg; MIP <−30 cm H ₂ O; MEP <40 cm H ₂ O; severe dysphagia	Consider tracheal intubation and mechanical ventilation

Figure 15.1 Decision-making algorithm in neurological patients with ARF

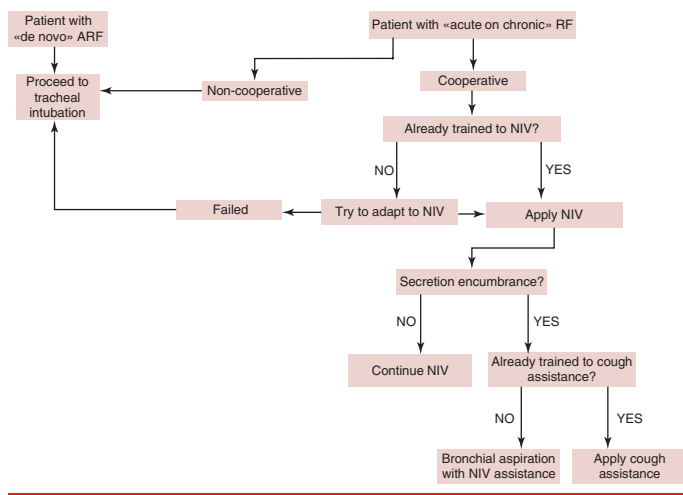


Figure 15.1 shows a decision-making algorithm for interventions at ER in patients with neurological disease and ARF.

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16. Neurological Emergencies in Pregnancy and Puerperium

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Introduction

Pregnant and post-partum women (Table 16.1) with acute neurological symptoms are a particularly sensitive group of patients whose diagnostic and therapeutic management must also take into account the health of the product of conception or the baby, in the case of breastfeeding.

The acute neurological symptoms that occur in pregnant and post-partum women may be:

Table 16.1 Definitions

Pregnancy or gestation: state of the woman who carries the product of conception into her uterus

Post-partum: a period that begins immediately after the expulsion of the foetal appendages and ends 2 h later; post-partum does not belong to the stages of childbirth and is instead the first stage of puerperium

Puerperium: period between the expulsion of the placenta and the return of the uterus to a normal pregestational state, usually lasts from 6 to 8 weeks

Pre-eclampsia (also known as **toxaemia**): is a syndrome characterized by the presence of *arterial hypertension, proteinuria and oedema*, after the twentieth week of gestation, in women previously normotensive. The frequency of this condition is 2–8% of pregnancies. Diagnostic criteria for *mild* pre-eclampsia, PA $\geq 140/90$ and proteinuria ≥ 0.3 g over 24 h; *severe*, at least two episodes of arterial hypertension with values $\geq 160/110$ at a distance of at least 6 h, proteinuria ≥ 5 g over 24 h and at least one sign of organ damage

Eclampsia: is a serious, potentially lethal pathology of pregnancy, characterized by the symptoms/signs of pre-eclampsia associated with *convulsions*. It represents the most fearsome complication of preeclampsia. The eclamptic syndrome can occur before, during or after childbirth. In most cases, eclampsia is preceded by signs of pre-eclampsia, in particular, hypertension and proteinuria. The only characteristic sign of eclampsia is the appearance of eclamptic convulsions: generalized tonic-clonic seizure, lasting only a few minutes. Besides seizures, the following symptoms may occur:

- Visual symptoms (scotoma, flashing lights, blurred vision)
 - Persistent headache in the occipital or frontal area
 - Confusion
 - Disturbances in consciousness up to coma
 - Localized abdominal pain in the right epigastrium or hypochondrium
-

- The manifestation of a pre-existing neurological disorder that worsens
- The first manifestation of a pathology not related to pregnancy
- An acute neurological disorder that occurs most frequently during pregnancy and puerperium

Since this is an extremely vast chapter, we have chosen to give greater emphasis to acute neurological pathologies that occur more frequently during pregnancy and puerperium, thus focusing on diagnostic algorithms that have already been dealt with in other chapters, where the fact that the patient is a pregnant woman or a woman who has recently given birth can significantly modify the diagnostic and therapeutic path in an emergency.

Besides, an ad hoc space has been dedicated to neuroradiological examinations and therapies during pregnancy and puerperium.

Pathophysiology

Several pathophysiological factors predispose pregnant and post-partum women to acute neurological diseases.

High oestrogen values stimulate the production of coagulation factors, increasing thromboembolic risk. At the same time, the increase in plasma and blood volume promotes the development of hypertension. The increase in progesterone concentration during late pregnancy tends to increase the relaxation of the venous walls and the risk of bleeding of small arterial blood vessels.

In the post-partum period, on the other hand, there is a fall in high oestrogen levels. The combination of these hormonal variations can result in increased capillary permeability and vasogenic oedema.

The pregnancy condition changes oestrogens and progesterone blood concentration, modifies the cerebral vascular reactivity and increases blood pressure; these alterations can determine modifications of the cerebral bioelectric activity and/or of the cerebral circulation, causing epileptic seizure, transitory or permanent cerebral ischaemia, intracerebral or subarachnoid haemorrhages and cerebral venous thrombosis.

Pre-eclampsia/eclampsia is a syndrome unique to human pregnancy and is the most pregnancy-specific cause of acute neurological manifestations. The key feature in the pathogenesis of pre-eclampsia/eclampsia seems to be the development of an abnormal placenta with fibrous and narrow spiral arteries. The hypoperfused placenta starts to deliver proinflammatory proteins that cause endothelial cell dysfunction and that lead to increased vascular permeability, vasoconstriction and formation of thrombi. The effects of endothelial injury are at the base of the main clinical manifestations of this syndrome. Vasoconstriction and vascular permeability can lead to acute neurological manifestations such as reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES) [1].

Neurological Syndromes

The most frequent neurological disorders during pregnancy are often secondary to:

- Cerebral venous thrombosis (CVT)
- Reversible cerebral vasoconstriction syndrome (RCVS)
- Posterior reversible encephalopathy syndrome (PRES)
- Neurological complications from eclampsia
- Other rare causes of acute neurological deficit:
 - Amniotic fluid embolism
 - Choriocarcinoma
 - Gas embolism
 - Wernicke's encephalopathy
 - Thrombotic thrombocytopenic purpura
 - HELLP syndrome
 - Pituitary apoplexy
 - Chorea gravidarum

Below is a brief description of the clinical pictures that will be used as a reference for the algorithms.

- **CVT.** It represents an important cause of stroke to be considered especially in women during pregnancy or post-partum. A peak in incidence in the first trimester may be attributable to women who become pregnant with underlying thrombophilia, but more than 75% of CVT cases are post-partum. Risk factors include caesarean section, dehydration, traumatic delivery, anaemia, high concentrations of homocysteine and intracranial

hypotension related to inadvertent dural puncture under epidural anaesthesia. CVT is more common in poor countries due to the increased frequency of malnutrition, infection and dehydration. Patients with CVT who are pregnant or taking oral contraception generally have a better long-term prognosis than patients with CVT who are not pregnant. Most patients have a diffuse, progressive and continuous headache, although 10% have a strong, piercing headache. Other symptoms include dizziness, nausea, seizures, papilloedema, signs of laterality, lethargy and coma. The specific presentation depends on the size and position of the dural sinuses and draining veins involved, side circles, effects on intracranial pressure and any associated haemorrhages or cerebral venous infarctions. Symptoms vary and may change over time. Without contrast medium, computerized tomography (CT) of the brain is often negative, but 30% of cases may show indirect signs of thrombosis or infarction. Venous infarctions often undergo a haemorrhagic transformation. Cerebral magnetic resonance imaging (MRI) with *spin-echo* sequences is the first-choice diagnostic investigation in the diagnosis of CVT.

- **RCVS.** It is characterized by abrupt onset of thunderclap headaches. Recurring daily thunderclap headaches over several weeks after a single thunderclap headache is nearly pathognomonic. Headache is often accompanied by vomiting, confusion, photophobia and changes in vision. Headache in RCVS can be mistaken for a sentinel headache from subarachnoid haemorrhage. The recurrence helps in differential diagnosis. When epileptic seizures or focal neurological deficits develop, they usually follow the headache. Symptoms usually regress in 2–3 months. Two-thirds of patients with RCVS develop symptoms within a week of giving birth and after a normal pregnancy. RCVS is associated not only with the post-partum condition but also with the use of immunosuppressive drugs, vasoactive substances (including serotonin reuptake inhibitors, cocaine and phenylpropanolamine), various other drugs, endogenous substances, catecholamine-secreting tumours, craniocervical arterial dissections and other conditions. Although in most cases RCVS has a favourable outcome, there is a variability of evolution up to the fatal outcome described in post-partum patients. The most frequent complications are subarachnoid haemorrhages followed by intracerebral haemorrhages and cerebral ischaemia. Haemorrhagic complications

usually precede ischemic complications. In patients without brain infarction or haemorrhagic complications, the disease resolves spontaneously. A small percentage of patients with RCVS also have cervical-cranial arterial dissections. Unless a haemorrhagic complication is present, the cerebrospinal fluid is usually normal but may show a low number of lymphocytes and a slight increase in proteins. In the absence of bleeding, brain CT is usually normal. Concerning neuroradiological investigations, it is important to recognize that RCVS is a dynamic process. TCD and direct or indirect angiographic evaluations (angio-CT and angio-MRI) are useful but may result normal during the disease in some cases. Direct angiography may reveal multifocal and segmental arterial vasoconstriction after the third day and can detect arterial dissections. Non-invasive investigations such as CT or MRI with angiographic sequences are positive in about 80% of patients and, at times, may show areas of alternating dilation and arterial vascular constriction that may be indistinguishable from those observed during vasculitis. Transcranial Doppler can be used to follow the resolution of the vasoconstriction.

- **PRES.** It is a syndrome characterized by headache, convulsions, encephalopathy and visual disturbances due to reversible vasogenic oedema evidenced by neuroradiological investigation (CT or MRI) of the brain [2]. PRES can occur in patients with acute arterial hypertension, pre-eclampsia or eclampsia, renal disease and sepsis and in subjects treated with immunosuppressants and other drugs. Symptoms develop without prodromes and progress rapidly in 12–48 h. About 90% of patients have focal and secondary generalized tonic-clonic seizures; seizures are generally preceded by changes in vision with blurred bilateral vision and headache. Severe symptoms can also occur in the absence of severe hypertension. Concerning the location of vasogenic oedema, which is located predominantly at the occipital lobe, about 40% of patients have visual symptoms such as visual hallucinations, blurred vision, scotomas and diplopia; 1–15% of patients have transient cortical blindness. The retina and pupils are normal. Many patients are confused and have memory loss. EEG (electroencephalogram) monitoring can detect epileptiform activity. CT will only show oedema in 50–60% of patients. Patients should have an MRI when PRES is

suspected. Brain MRI reveals focal oedema, most frequently in parietal and occipital lobes. Unlike ischemic lesions of the posterior cerebral artery, occipital lesions spare the medial occipital lobe and the calcarine cortex. About one-third of patients have oedema in other areas of the brain, but almost all have concomitant posterior involvement. Visual symptoms often resolve completely in hours or days; the resolution of neuroradiological oedema takes longer than the resolution of the clinical manifestations. Rarely, pregnant or post-partum women develop PRES for other reasons (such as drugs or RCVS) and not as a result of eclampsia [3]. Thus, although there is overlap in most patients, eclampsia and PRES can occur independently. Studies comparing the clinical and radiological characteristics of PRES in nonpregnant patients with those of pregnant patients have shown mixed results. PRES and RCVS partly share the same risk factors and may co-exist. PRES lesions are not always reversible if the factors that determine PRES are not removed.

- **Neurological complications from eclampsia.** Epileptic seizures are a characteristic sign of eclampsia. Eclamptic seizures are usually generalized tonic-clonic and last about 1 min. Symptoms that may precede seizures include persistent frontal or occipital headache, blurred vision, photophobia in the upper right quadrants or epigastric pain and altered consciousness. In about one-third of cases, no arterial hypertension or proteinuria is reported before the epileptic seizure. There are several hypotheses about the mechanism of eclamptic convulsions: altered cerebral vascular self-regulation in response to hypertension could lead to arterial vasospasm and subsequent ischaemia with cytotoxic oedema; alternatively, loss of self-regulation in response to hypertension could lead to endothelial dysfunction, increasing capillary permeability with vasogenic oedema; this vasculopathy can also cause PRES or ischemic and haemorrhagic lesions. Although the focal vasogenic oedema is characteristic of eclampsia, up to a quarter of patients have areas of persistent cytotoxic oedema, corresponding to ischaemia or focal haemorrhage. Therefore, the areas of ischaemia or haemorrhage of PRES and also of RCVS can contribute to eclamptic seizures. About 90% of eclampsia cases occur at or after 28 weeks of gestation. Just over a third of eclamptic crises

occur at the end and can develop intrapartum or within 48 h of childbirth. The so-called late or post-partum-eclampsia, i.e. eclampsia that starts more than 48 h after the birth, is increasingly reported. In a large post-partum eclampsia study, two-thirds of patients were discharged and readmitted due to late post-partum symptoms of pre-eclampsia, most commonly headache. The percentage of pre-eclampsia and eclampsia diagnosed after childbirth is 11–55%, and the figure could increase with better prepartum recognition. Post-partum women sometimes ignore symptoms, such as headache or abdominal pain, and seek medical attention only after seizures. Patients with post-partum eclampsia, especially those with delayed post-partum eclampsia, have a higher incidence of cerebral venous thrombosis, cerebral haemorrhage and acute cerebral ischaemia than patients with prepartum diagnosis. Although most women with typical eclampsia do not need brain neuroradiological investigations, after delivery eclamptic patients, those with focal neurological deficits, persistent visual disturbances and magnesium refractory symptoms, should undergo a comprehensive diagnostic evaluation, preferably including a brain MRI. Neuroradiological investigations may also reveal areas of vasoconstriction consistent with RCVS, and, rarely, pregnant patients, especially those with RCVS, may develop craniocervical arterial dissections. Neuroradiological findings in patients with pre-eclampsia and eclampsia include infarction, haemorrhage, vasoconstriction, dissection and vasogenic and cytotoxic oedema.

Other Rare Causes of Acute Neurological Deficit

Amniotic fluid embolism and **metastatic choriocarcinoma** are two specific conditions of pregnancy that can occur with neurological symptoms. Amniotic fluid embolism causes agitation, confusion, convulsions, encephalopathy and cardiovascular and respiratory failure during or immediately after delivery. Choriocarcinoma is a rare trophoblastic tissue tumour and is complicated with metastasis to the brain in 20% of patients. Since the tumour can cause mass effect, bleed and invade multiple brain vessels, the clinical manifestations and the neuroradiological diagnosis can be varied.

Gas embolism occurs when the air that enters the myometrium during childbirth passes through the venous circulation to the right ventricle, causing a reduction in cardiac output and the resulting seizures and changes in the state of vigilance, during the delivery phase or immediately after. Almost any focal or generalized neurological symptom can also occur due to gaseous shunts between the right and left intracardiac through a patent foramen ovale. The presence of air in the retinal veins and the so-called “mill-wheel” heart murmur suggest the diagnosis.

Wernicke’s encephalopathy can complicate hyperemesis in pregnancy. In a study of 625 patients with Wernicke’s encephalopathy not related to alcohol abuse, 76 women (12%) had hyperemesis. Abnormal eye movements are almost always present, but the classic triad of confusion, eye manifestations (e.g. diplopia and nystagmus) and gait abnormalities occurs in a minority of patients. Some patients have an otherwise unexplained metabolic acidosis. Haematological investigations are not necessary for the diagnosis, but the clinical response to intravenous thiamine administration is sufficient. The brain MRI study in Wernicke’s suspected encephalopathy appears indicated.

Pregnant women are particularly at risk for **thrombotic thrombocytopenic purpura** (TTP), which most commonly occurs at the end of the second or beginning of the third trimester. The classical manifestations include thrombocytopenia, microangiopathic haemolytic anaemia, fever and neurological and renal dysfunction. Neurological manifestations, which are present in more than half of the patients, include remitting headache, epileptic seizures and focal and/or generalized neurological deficits. The presence of PRES is common in these patients. The differential diagnosis with the HELLP syndrome is important; this is a particular form of pre-eclampsia, described in 1982 by Weinstein as a nosological entity whose acronym derives from the symptomatological triad “Hemolysis, elevated Enzymes Liver and Low Platelet count”. HELLP appears in the third trimester of pregnancy and/or in the first weeks after delivery, although in about 11% of patients it occurs from the 27th week of gestation. It often appears in conjunction with a typical picture of pre-eclampsia but sometimes even in the absence of hypertension, with an incidence ranging from 0.2% to

0.6% of pregnant women. In comparison, eclampsia has an incidence of 5–10%. HELLP occurs between 4% and 12% of patients with pre-eclampsia or eclampsia. It presents a high risk of morbidity and maternal mortality. When it occurs in post-partum, the onset occurs within 48 h after the birth, but also 7 days later, following a pregnancy conducted without apparent complications. The syndrome may originate from common pathogenic mechanisms (endothelial damage, vasospasm, alteration of the vasoconstrictor/vasodilator ratio) responsible for a variable spectrum of pathological manifestations in pregnancy or post-partum. The variety of the onset can make the diagnosis difficult: about 90% of patients have general malaise, 65% epigastric pain, 30% nausea and vomiting and 31% headache. Moreover, scotomas, dyspnea, jaundice, hypertension and proteinuria may occur. Since early diagnosis is difficult, all pregnant women with general malaise or suggestive symptoms of viral infection in the third trimester should check for blood count and liver function.

The three main alterations found in HELLP are haemolysis, the elevation of liver enzymes and the reduction of platelets. Mortality in women with HELLP is about 1.1%, while neonatal mortality ranges from 8% to 22–24%. 1–25% of patients with HELLP experience complications such as CID, placenta detachment, ARDS, hepatorenal syndrome, subcapsular haematoma and liver rupture; the foetus frequently experiences growth retardation and respiratory distress.

Pituitary apoplexy, acute infarction or bleeding of the gland often in the context of a previous failure to diagnose adenoma, occurs with headache, changes in vision, ophthalmoplegia and reduced state of vigilance and consciousness. Although a slight enlargement of the pituitary gland occurs during pregnancy, pregnancy itself is rarely the cause of pituitary apoplexy. Pituitary apoplexy is distinguished from Sheehan's syndrome (ischemic pituitary necrosis, characterized by pituitary insufficiency—hypopituitarism—with appearance weeks or months after severe post-partum haemorrhage) and lymphocytic pituitary disease (headache and visual symptoms that present sharply in pregnant patients but generally with a slower onset than in nonpregnant patients). Brain MRI is usually diagnostic.

Chorea gravidarum is a condition characterized by irregular, short and unpredictable jerky movements of several parts of the body that rarely lead to be life-threatening. This condition is often associated with other conditions during pregnancy such as rheumatic fever, antiphospholipid antibody syndrome, stroke, Wilson's disease and thyrotoxicosis and generally begins after the first trimester but may occur after childbirth. The symptoms usually resolve spontaneously within a few weeks or months, or they may settle after childbirth. Also in this case, the brain MRI can be indicated.

The main clinical characteristics of the conditions listed above at onset and the diagnostic indications are summarized in Table 16.2.

Diagnostic Algorithms

For the diagnostic framework and the definition of the paths of the main emergencies/urgencies during gestation or immediately after childbirth, we used data based on the evidence available in the literature.

The main clinical expressions of acute neurological diseases in pregnant and post-partum women are often overlapping, and different diseases may also coexist. However, details, such as the characteristics of the headache, the evolution of symptoms over time and the frequency of certain symptoms such as convulsions or visual disturbances, may help to establish the diagnosis.

Seizure Algorithm

Pregnant or post-partum women with seizures can be divided into three categories:

1. Patients **suffering from epilepsy** before pregnancy, more frequent occurrence.
2. Patients with a **new epileptic disorder not etiologically linked** to pregnancy (e.g. epileptic seizures from unknown cerebral neoplasia or from hypoglycaemia).

Table 16.2 Clinical characteristics at onset and diagnostic indications of specific neurological emergencies in pregnancy and post-partum

	Onset with acute neurological deficit	Onset with epileptic seizures	Onset with headache	Initiation mode	Evolution
Eclampsia		✓	✓	A	↓/=
CVT	✓	✓	✓	A/W	↓
PRES	✓	✓	✓	A	↓
RCVS			✓	A	=
Ischaemia and/or cerebral haemorrhage/ESA	✓	✓	✓	A/W	↓
PTTC or HELLP	✓	✓	✓	A/W	↓/=
Wernicke's Encephalopathy	✓			W	=/↓
Chorea gravidarum	✓			W	=/↑
Pituitary apoplexy			✓	A/W	=/↓
Gas and amniotic fluid embolism	✓			A	↓/=

Laboratory diagnosis	Cerebrospinal fluid	EEG	Neuronological diagnosis	Neuroradiological diagnosis	Other
Yes proteinuria	n.s.	Yes	n.s.	No.	Response to MgSO_4
n.s.	Possible intracranial hypertension	No	n.s.	MRI	MRI
n.s.	n.s.	No	n.s.	MRI	MRI
n.s.	Possible pleocytosis and protein \uparrow	No	Extra and intracranial ultrasound	Angio-MRI	Angio-MRI
n.s.	n.s. (except ESA)	No	Extra and intracranial ultrasound	TC/MRI	TC/MRI
Blood count and biochemical tests	n.s.	No	n.s.	MRI	MRI
Blood count and biochemical tests	n.s.	No	n.s.	n.s.	Thiamine response
n.s.	n.s.	No	n.s.	n.s.	n.s.
Hormone dosage	n.s.	No	n.s.	MRI	MRI
n.s.	n.s.	No	n.s.	MRI	MRI

Onset: A acute, W worsening in hours or days. *Evolution:* \uparrow improvement, = stable, \downarrow worsening, n.s. not significant

3. Patients who have **a new epileptic seizure etiologically related to their** pregnancy (e.g. seizures caused by eclampsia, cerebral haemorrhage, CVT, RCVS, PRES, PTT). While in PRES patients seizures are frequent and generally occur at the onset of the disease without prodromal symptoms, in case of CVT, seizures tend to occur later and almost always after the headache; brain CT can be normal in both conditions. Epileptic seizures are much less common in the case of RCVS.

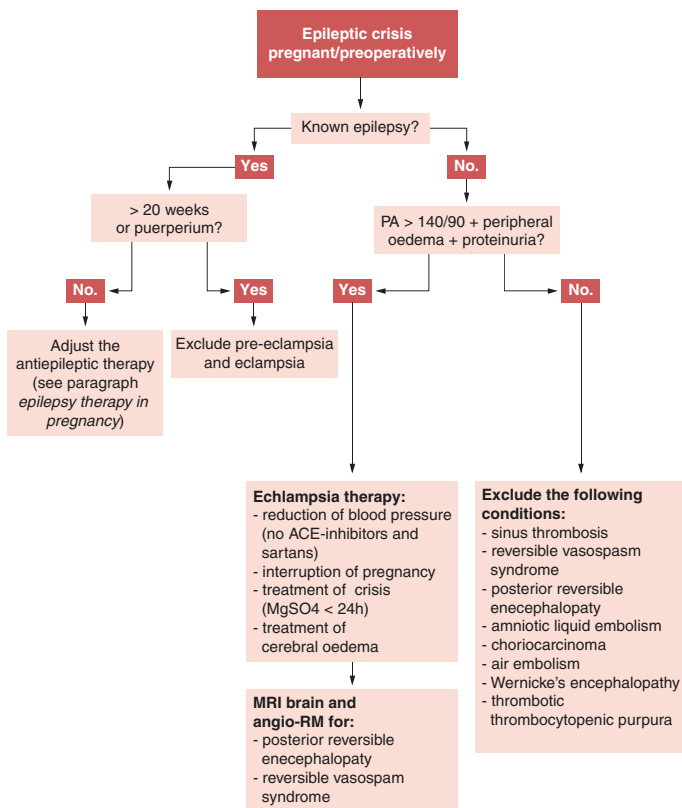
With regard to pregnant and post-partum women belonging to the first two categories, the diagnostic approach does not differ from the systematic one that is implemented in all patients with new epileptic seizures. For women belonging to the third category, however, there is still not enough literature data to determine which is the best initial workup. However, considering that there is a wide spectrum of differential diagnoses and that the sensitivity of brain CT is low, it is desirable that all pregnant and post-partum women with newly emerging epileptic disorder undergo extensive diagnostic investigations, including usually brain MRI, in order to determine the cause of seizures. The only exception to the routine execution of neuroimaging is represented by those patients whose seizures are compatible with a typical prenatal eclampsia, in that case it will be necessary to proceed to the specific treatment of the same.

The algorithm on seizures in pregnant women and women who have recently given birth is shown in Fig. 16.1.

Therapeutic Approach

Therapy of epilepsy in pregnancy. Epilepsy does not seem to significantly alter female fertility rate, and it is estimated that a proportion ranging from 0.2% to 0.7% of pregnant women are affected by this disease [4]. During pregnancy, in most women with epilepsy, there are no changes in the frequency of seizures. However, in 15–30% of cases [5–8] an increase in frequency can be observed, probably linked to the effect of oestrogen and progesterone on neuronal excitability.

Figure 16.1 Seizure algorithm



Other factors related to pregnancy that may worsen seizure control include lack of sleep, stress and anxiety, changes in the pharmacokinetics of antiepileptic drugs (FAEs), decreased compliance with therapy due to teratogenicity concerns or a shift to less effective drugs because they are considered to be less teratogenic [9].

Crisis control before pregnancy is probably the most important predictive factor of crisis control during pregnancy. In fact, women who have no seizures in the 9 months preceding pregnancy have a high probability of remaining free from seizures during pregnancy [7].

The frequency of seizures during delivery or in the following 24 h is reported to be about 2.5%, with a higher risk when the control of seizures in pregnancy has been incomplete [10].

The management of pregnancy in epileptic women is complex and requires a multidisciplinary approach and coordination between different specialists (epileptologist, gynaecologist, teratologist, geneticist, neonatologist, and paediatrician).

Pharmacological therapy is the cornerstone of the treatment of epilepsy, but does not allow adequate control of seizures in about 15–20% of cases.

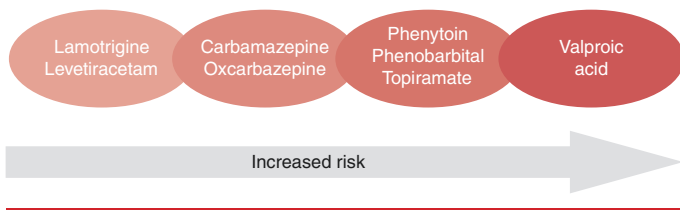
A good control of seizures in pregnancy is essential because, especially in generalized tonic-clonic seizures and status epilepticus, they are associated with maternal and foetal complications (hypoxia and maternal and foetal acidosis, abortion and threatened premature birth, intracranial foetal haemorrhage and foetal bradycardia, foetal intrauterine death and death of the mother).

The incidence of congenital malformations among children of epileptic mothers is about 2–3 times higher than in the general population [11]. Although it has been hypothesized that epilepsy itself increases the risk of malformations, it is now believed that this increase in birth defects is mainly due to antiepileptic therapy.

Maternal and foetal risks associated with poor control of pregnancy seizures are now considered greater than those associated with drug treatment, and therapy is therefore generally indicated, especially if the woman has seizures before pregnancy.

Pharmacological therapy must be constantly monitored, as pregnancy leads to significant changes in the pharmacokinetics of drugs (absorption, distribution and elimination) [12] and consequently changes in their plasma concentration, sometimes clinically relevant. In most cases, the plasma concentration of antiepileptic drugs decreases during pregnancy and quickly returns to prenatal values after childbirth.

Figure 16.2 **Teratogenic risk profile of antiepileptic drugs (including data on major foetal malformations, foetal growth and cognitive outcomes, where available) [13]**



Different types of drugs are administered in mono or polypharmacy, depending on the type of epilepsy, the severity of the disease and the patient's response to the therapy itself. While it is not foreseeable that a foetus will be less or more susceptible to develop malformations when exposed to a given drug, it has been shown that there are drugs (such as phenytoin and valproic acid) that carry a higher risk of foetal damage than others (such as carbamazepine) (Fig. 16.2).

In general it is advisable to:

- Prescribe the most effective medication for the patient and with the lowest maternal-foetal risks.
- Administer the medications of which you have the greatest clinical experience (e.g. for the longest time on the market) and at the lowest effective dosage.
- Take the medication in monotherapy.

Attention, please:

- The administration of several antiepileptic drugs during pregnancy is associated with an increased teratogenic risk.
- Most antiepileptic drugs cause a decrease in plasma levels of folates. Adequate supplementation of folic acid (4–5 mg/day) is therefore recommended during preconception (2–3 months) and pregnancy.

Classic antiepileptic drugs (in order of choice):

- Benzodiazepines (including diazepam, clonazepam and clobazam)
- Carbamazepine
- Ethosuximide
- Barbiturates (phenobarbital and primidone)
- Phenytoin
- Valproic acid (avoid if possible)

Attention, please:

Excluding benzodiazepines (in general), carbamazepine is the classic antiepileptic drug for which, to date, fewer teratogenic effects have been shown.

New antiepileptic drugs (in order of choice):

- Lamotrigine
- Levetiracetam
- Topiramate
- Gabapentin
- Vigabatrin
- Oxcarbazepine
- Pregabalin
- Felbamate

Attention, please:

- Studies available in the human field on the effects of the use of new antiepileptic drugs are scarce to date.
- Lamotrigine is the new-generation antiepileptic drug for which, to date, fewer teratogenic effects have been shown.

Therapy of epilepsy during breastfeeding. The maternal intake of antiepileptic drugs in monotherapy is in most cases compatible with breastfeeding. In the case of polypharmacy, the risk of possible effects on the infant should be assessed on a case-by-case basis.

Classic antiepileptic drugs (in order of choice):

- Drugs compatible with breastfeeding (in monotherapy):

- ☐ Carbamazepine
- ☐ Valproic acid
- ☐ Phenytoin

Attention, please:

- Clinical monitoring of the infant and, if necessary, control of liver function (carbamazepine) are required.
- In the case of polypharmacy, the decision to breastfeed during treatment should be carefully considered on a case-by-case basis.
- Drugs to avoid:
 - ☐ Barbiturates (phenobarbital and primidone)
 - ☐ Ethosuximide
 - ☐ Benzodiazepines (including diazepam, clonazepam, and clobazam)

New antiepileptic drugs:

- Drugs compatible with breastfeeding (in monotherapy):
 - ☐ Lamotrigine
 - ☐ Levetiracetam
 - ☐ Topiramate
 - ☐ Gabapentin
 - ☐ Vigabatrin
 - ☐ Oxcarbazepine
 - ☐ Pregabalin

Attention, please:

- Studies available in the human field on the effects of the use of new antiepileptic drugs are scarce to date.
- The new antiepileptic drugs tend to pass into milk in greater quantities than the classic antiepileptic drugs.
- In monotherapy they are generally compatible with breastfeeding; however, adequate clinical monitoring of the infant (and possibly serum dosage of the drug) is necessary.
- In the case of premature babies and polypharmacy, the decision to breastfeed during treatment should be carefully considered on a case-by-case basis.
- Drugs to avoid:
 - ☐ Felbamate

Headache Algorithm

Primary headaches, particularly migraine and tension-type headache, are the most common forms of headache in both pregnancy and post-partum. Paradoxically, this makes the diagnosis more difficult if one does not pay much attention to some features of the headache that help suspecting a secondary form. In the case of isolated headache, i.e. not associated with focal neurological signs or symptoms or fever or altered consciousness, it is therefore necessary to remember to specifically ask patients about the so-called *red flags*:

- Is this a **severe headache with sudden onset** (*thunderclap headache*)?
- Is this a **new, unusual headache** the patient has never experienced?
- Has there been a **change in the usual pattern** of headache?
- Is there **hypertension**?
- Does the patient have a **history of previous cerebrovascular disease**?

It is estimated that about 40% of post-partum women suffer from headache, often in the first week after delivery. **Migraine** generally improves during pregnancy but often recurs after delivery due to falling blood levels of oestrogen. Although migraine may begin during pregnancy, the clinician should be very cautious in making this diagnosis. The recurrence of several episodes (at least five migraine attacks and at least ten tension headache attacks) is essential to make a diagnosis; therefore, after the first attack of a new headache arising during pregnancy, it is not possible to make a definitive diagnosis of primary headache.

Patients with pre-eclampsia often have a pulsating, bilateral headache, which can be accompanied by blurred vision and scintillating scotomas.

All pregnant women with a new headache should be screened for pre-eclampsia. It may be associated with hypertension, oedema, pain in the epigastrium or in the right hypochondrium, osteotendinous hyperreflexia, proteinuria and, occasionally, restlessness or agitation. Other alterations in haematochemical tests that cause

concern in patients with pre-eclampsia are thrombocytopenia, haemoconcentration, high level of transaminases and creatinine.

Patients with the so-called *thunderclap headache* require specific investigations as soon as possible.

All patients with severe rapid onset should undergo careful investigations to rule out subarachnoid haemorrhage: generally a brain scan CT and, if negative, a lumbar puncture should be performed. If the investigations do not show subarachnoid haemorrhage, other diseases such as PRES, CVT, RCVS and extra- or intracranial arterial dissection should be considered. If brain CT and lumbar puncture are negative in the presence of strong clinical suspicion, brain MRI with DWI sequences and sequences for the study of both arterial and venous circulation may be indicated.

In the post-partum period, **primary headaches** are frequent; a study of 95 patients with severe post-partum headache, resistant to standard treatments, showed that 39% of the cases were tension-type headache, 24% had a pre-eclampsia or eclampsia state, 16% were postpuncture headache during epidural anaesthesia, 11% were migraine headaches, 3% were secondary to pituitary haemorrhage or thrombosis of the venous sinuses, while in 1% of cases there were expansive brain lesions.

In patients under spinal anaesthesia, it is important to remember the possibility of **postpuncture dural headache**. This headache is part of the so-called CSF hypotension syndrome, caused by reduced intracranial pressure due to loss of CSF, often has a nuchal and occipital localization, typically begins 1–7 days after delivery, worsens with erect station and resolves after 10–15 min that the patient remains lying down. Tinnitus, hypoacusis and diplopia can be associated. The incidence of headache after spinal cord puncture (PDPH) is about 0.5–1.5% of women under spinal anaesthesia; headache usually resolves within 48 h in patients undergoing epidural *blood patch* procedure. Women who have not undergone spinal anaesthesia may rarely have CSF hypotension headache, due to hard push lacerations during delivery. Although in most cases CSF hypotension headache is resolved without consequences, it is worth remembering some rare complications such as subdural

haematomas, PRES and CVT. Intracranial hypotension can cause subdural haematomas probably by stretching laceration of the cerebral bridge veins. In these patients the postural characteristic of headache may be absent because the intracranial hypotension caused by the loss of CSF is compensated by an increase in intracranial pressure secondary to haematoma. Another diagnostic clue is the lack of response to treatment with *blood patch*. For the correct diagnosis of CSF hypotension syndrome, brain MRI with gadolinium is indicated.

In most cases, secondary headaches are more likely to occur in the post-partum period than during pregnancy; therefore, the physician should always consider the possibility of a headache secondary to one of the above severe causes in cases where the clinical-anamnestic picture makes migraine or post-dural-puncture headache (PDPH) unlikely.

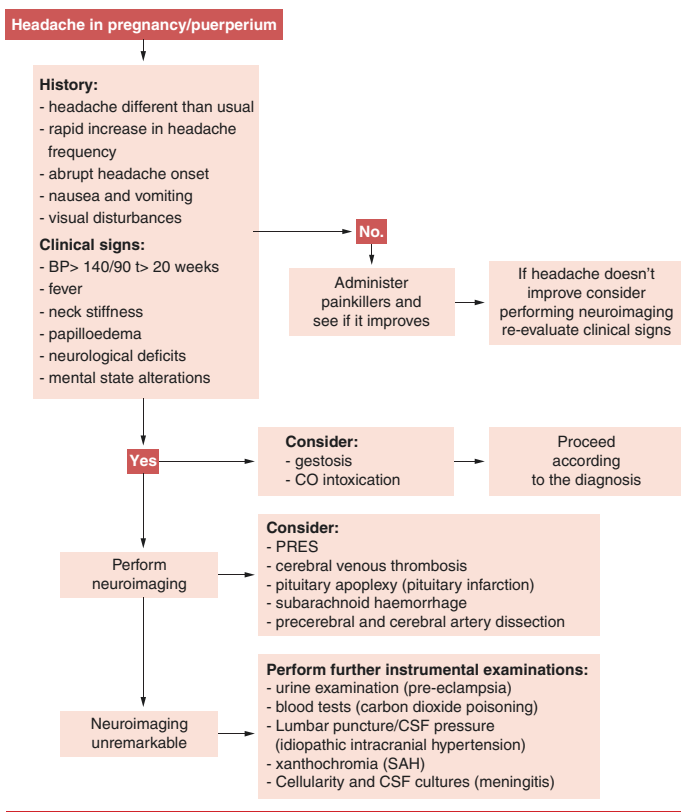
The algorithm for headache during pregnancy and puerperium is shown in Fig. 16.3.

Therapeutic Approach

Migraine therapy. The treatment of migraine in pregnancy is indicated because maternal and foetal complications related to the disease can be more harmful than therapy, especially if migraine attacks are frequent, severe and associated with nausea, anorexia, vomiting, hypotension or dehydration. Since most women have symptoms that fade away or disappear after the first trimester of pregnancy, the therapy can often be changed during the course of the pregnancy until it is discontinued.

The *first-choice therapy is the non-pharmacological therapy*: rest avoiding environmental factors and triggering foods, biofeedback, ice, relaxation techniques and acupuncture. If non-pharmacological therapy is not sufficient, it is possible to prescribe some of the drugs approved in the guidelines for the treatment of migraine, taking into account the fact that for most of them human studies on the effects of taking them during pregnancy are insufficient (www.farmaciegravidanza.gov.it).

Figure 16.3 Headache algorithm



In general it is advisable to:

- Prescribe the most effective medication for the patient and with the lowest mother-foetal risks.
- Administer the medications of which you have the greatest clinical experience (e.g. for the longest time on the market) and at the lowest effective dosage.
- Take the medication in monotherapy.

Symptomatic therapy of migraine in pregnancy. Pharmacological therapy includes in order of risk-benefit ratio (lower risk and maximum efficacy):

- Paracetamol: avoid administration in association with pseudoephedrine, acetylsalicylic acid or other NSAIDs.
- Acetylsalicylic acid.
- Ibuprofen.
- Indomethacin.
- Sumatriptan.

Attention, please:

NSAIDs (acetylsalicylic acid, ibuprofen and indomethacin) are to be avoided in the third trimester of pregnancy due to their effects on foetal circulation.

In case of nausea and/or vomiting, the drugs in order of risk-benefit ratio (lower risk and maximum effectiveness) are:

- Pyridoxine (vitamin B6)
- Promethazine and dimenhydrinate
- Prochlorperazine and chlorpromazine
- Metoclopramide

Attention, please:

- In case of ineffectiveness of the previous ones, domperidone can be used.
- For newly marketed drugs such as ondansetron, there are not enough data, and therefore they should be avoided.
- If the symptoms persist and do not respond to the treatments listed above, methylprednisolone.

Prophylactic therapy during pregnancy. It is advisable to prescribe prophylactic therapy if there are three or more severe migraine attacks per month, which are particularly disabling and do not respond to symptomatic treatment.

A non-pharmacological approach would be preferable, but, if not effective, the following are indicated:

- B-blockers (propranolol and metoprolol) in low doses, for migraine without aura
- Amitriptyline for migraine without and with aura

Attention, please:

- B-blockers taken during the third trimester of pregnancy may induce bradycardia, hypotension and foetal/neonatal hypoglycaemia.

- Amitriptyline may be associated with withdrawal crises or signs of neonatal *distress*. It is therefore necessary to closely monitor these signs and symptoms, in the prenatal and post-natal period.

Symptomatic therapy during breastfeeding Symptomatic therapy during breastfeeding:

- Paracetamol
- NSAIDS
- Sumatriptan

Attention, please:

- High-dose acetylsalicylic acid is contraindicated.
- Nimesulide and piroxicam are to be avoided.
- It is recommended to breastfeed 8 h after taking sumatriptan.

Prophylactic therapy during breastfeeding:

- Low doses of b-blockers, at the lowest possible effective dose (avoid atenolol and nebivolol).
- Amitriptyline should be used with caution for effects on the newborn (Table 16.3).

Acute Neurological-Deficit Algorithm

Pregnant or post-partum patients with persistent motor, sensory or visual symptoms at acute onset (with or without headache) generally need careful and urgent investigation to rule out the most serious causes.

Motor, sensory, visual or transient speech impairments in pregnant women are more likely to be due to **migraine with aura** even in the absence of headache. Some medical history clues may help the doctor to recognize a migraine disorder: neurological symptoms begin gradually and more often include positive phenomena (e.g. photopsias or glittering scotomas) rather than negative ones (e.g. negative scotomas or more rarely partial/total loss of the visual field). Positive symptoms (visual or sensory, such as tingling or a pinprick sensation) gradually spread and are often followed by loss of function (e.g. scotomas or numbness). Usually the symptoms are

Table 16.3 Risk profile for migraine medications in pregnancy and puerperium [14]

	Drugs before conception	I quarter	II quarter	III quarter	Breastfeeding
Symptomatic therapy					
Paracetamol	●	●	●	●	●
Sumatriptan	●	●	●	●	●
Other triptans	●	●	●	●	●
NSAIDs: ibuprofen, diclofenac, naproxen	●	●	●	●	●
Prophylactic therapy					
B-blockers: metoprolol, propranolol	●	●	●	●	●
Tricyclic antidepressants: amitriptyline	●	●	●	●	●
Antiepileptics: valproate	●	●	●	●	●
Antiepileptics: topiramate	●	●	●	●	●

● Considered safe

● Generally considered safe (uncertainty related to certain specific drugs in a class or a specific period of pregnancy or limited data)

● The increased risk of foetal harm cannot be excluded either because there are studies that reveal harmful effects or because data supporting safety is missing.

● Contraindicated

resolved in one mode (e.g. visual) and then develop in another mode (e.g. somatosensory or aphasic). On average, each symptom regresses in 20–30 min.

Since visual symptoms are frequent in pre-eclampsia, the diagnosis of migraine aura should not be made without taking into account other **diseases that may affect the visual pathways** such as PRES, pituitary apoplexy and stroke. Also to be considered are orbital haemorrhages that occur with acute diplopia, proptosis and eye pain, usually during the first trimester (from hyperemesis) or during childbirth (from thrust).

Brain stroke in pregnant and post-partum women is rare; however, the risk is greater than in non-pregnant women of the same age, especially in the period from the third trimester to the first 6 weeks after delivery, in relation to conditions of hypercoagulability [15, 16]. Clinical factors associated with an increased risk of stroke are present in 16–18% of Western women and 11% of Asian women under 35 years of age. In literature variables rates are reported of stroke in pregnancy and puerperium: it is estimated that for every 100,000 parts 4–11 ischemic strokes; 3.7–9 brain haemorrhages; 2.4–7 subarachnoid haemorrhages; and 0.7–24 thrombosis of the venous sinus occur.

Pre-eclampsia and eclampsia play a causal role in 25–50% of cases of ischemic stroke. Other risk factors for stroke are age, African-American race, hypertension and heart disease, caesarean section, migraine, thrombophilia, thrombocytopenia, sickle-cell anaemia and systemic lupus erythematosus. The presence of thrombocytopenia may also suggest the so-called *HELLP syndrome* (haemolysis, elevated liver enzymes, thrombocytopenia) or thrombocytopenic purpura, whose incidence is increased during pregnancy and whose clinical presentation may be similar to stroke. Another cause of stroke in pregnancy is the dissection of the cervical-cranial arteries, although there is no reliable epidemiological data showing an increased incidence of this disease in pregnant and post-partum women. Patients with cervical arterial dissection often have isolated nuchal headache without neurological deficits, but sometimes symptomatic brain attacks may occur. Possible causal factors are the Valsalva manoeuvre during childbirth or poor positioning of

Table 16.4 Some risk factors and causes of ischemic stroke in pregnancy and puerperium, according to TOAST 16 classification

Risk factors/causes	Period
Cardioembolism Cardiomyopathy <i>peripartum</i> Cardiomyopathy or heart failure Mechanical valves	First trimester and puerperium pregnancy and childbirth First trimester, third trimester, childbirth and puerperium
Aortic dissection	Childbirth
Coagulation disorders Antiphospholipid syndrome, lupus, sickle-cell anaemia, C/S protein deficiency, alterations of the Leiden V factor	Third trimester, childbirth and puerperium
Amniotic fluid embolism	Childbirth and puerperium
Pre-eclampsia and eclampsia, blood hypertension and HELLP syndrome	From the second quarter onwards
Migraine	Pregnancy
Infections	Puerperium

Modified by Adams et al. [17] and van Alebeek et al. [18]

the hyperextended neck patient during anaesthesia, although there is no evidence of this.

In patients (Table 16.4) with **cerebral haemorrhage and subarachnoid haemorrhage**, the presence of vascular malformations and aneurysms is relatively frequent. Subarachnoid haemorrhages occurring in the vicinity of the Willis circle are more often suggestive of the presence of aneurysms, while subarachnoid haemorrhages of the convexity more often suggest an RCVS or a CVT. Both heart attacks and brain haemorrhages can be caused by vasculopathies, including RCVS and pre-eclampsia. Finally, rare causes of stroke in pregnant and post-partum women include thrombotic thrombocytopenic purpura, pituitary apoplexy, amniotic embolism, choriocarcinoma, gas embolism, post-partum cardiomyopathy and cardioembolism. In these patients it is necessary to perform extensive diagnostic investigations, including vascular imaging, in order to identify the specific cause and then implement a specific treatment.

In the suspicion of stroke, both ischemic and haemorrhagic, for the availability and speed of execution, the diagnostic test most easily usable is the CT; when, and, if available, it would be preferable to perform an MRI with angio-MRI and sequence in diffusion (DWI), able to detect the presence of an extremely early cerebral ischaemia and to make a precise differential diagnosis without the use of contrast medium, also highlighting early any venous thrombosis, particularly fearsome in pregnant women [19]. With the SWI and gradient echo sequence, vessel analysis and the possible presence of hemosiderin deposits can help in the diagnosis of vascular dissection or bleeding, for example, in the context of cavernous angiomas.

In any case, MRI examination is desirable from the second trimester of pregnancy onwards (see specific section).

In acute ischemic stroke with MRI, mismatch DWI/FLAIR can be used to discriminate the “ischemic core” from the “penumbra” area, which is potentially recoverable/salvageable with intravenous fibrinolytic treatment or with intraarterial mechanical thrombectomy. Abnormalities in DWI correspond to the core and partly to the penumbra.

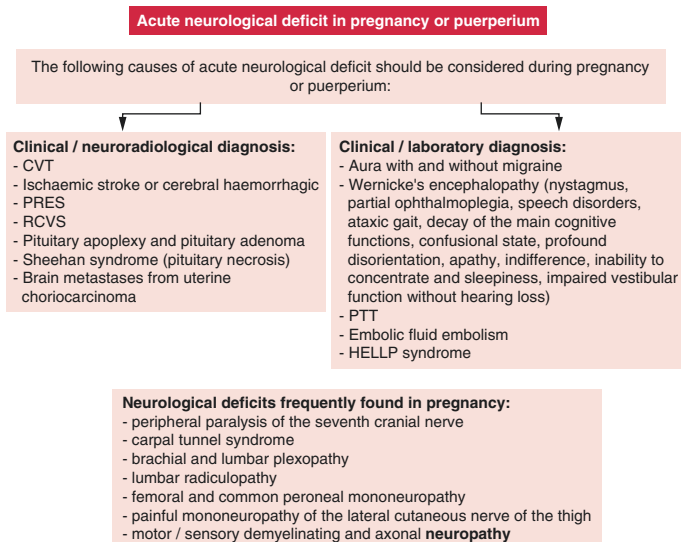
The algorithm for acute neurological deficit in pregnant women and women who have recently given birth is shown in Fig. 16.4.

Therapeutic Approach

Anti-Platelet Therapy

Acetylsalicylic Acid

Pharmacokinetic characteristics. Acetylsalicylic acid (ASA) belongs to the category of NSAIDs that inhibit prostaglandin synthesis by acting on the enzyme cyclooxygenase; at low doses it is used as an anti-platelet in the prevention of thrombotic events. It has a half-life of about 6 h, its metabolites of 3–12 h (depending on the dose) and passes the placental barrier.

Figure 16.4 **Acute neurological deficit algorithm**

The acute treatment with intravenous fibrinolysis (t-PA is non teratogenic and does not pass the placental barrier) and thrombectomy are contraindicated in the guidelines for the risk of placental bleeding and use of contrast medium; each clinical case should be considered individually.

CVT = Cerebral Venous Thrombosis

RCVS = Reversible Cerebral Vasoconstriction Syndrome

PRES = Posterior Reversible Encephalopathy Syndrome

TTP = thrombotic thrombocytopenic purpura

HELLP = hemolysis elevated liver enzymes low platelet count

- Low doses (75–100 mg/day)
- *Pregnancy trimester I:* data available in the human field, on large samples of women treated with low doses of ASA in pregnancy, have not so far shown an increase in congenital abnormalities in exposed births compared to expected. The sporadic reports of malformations in case reports are to be considered anecdotal because they do not have a specific pattern and have not been confirmed by subsequent epidemiological studies.
- *Second to third trimester pregnancy:* numerous studies have not shown, for maternal exposure at low doses, adverse foetal-neonatal effects. In particular, an increased risk of bleeding (intracranial, gastrointestinal, etc.) and changes in circulation

(closure of the Botallo duct) in the foetus/infant was not observed compared to what was expected. However, some authors suggest that therapy should be discontinued at least 5 days before the birth.

- Medium (>100–300 mg/day) and high doses (>300 mg/day)
- *Quarter I*: data available in the human field on large samples of women treated with this drug during pregnancy have not so far shown an increase in congenital abnormalities in exposed births compared to the expected. Some studies report an increased risk for gastroschisis, intestinal atresia and cryptorchidism in foetuses/infants exposed to analgesic substances in combination (including paracetamol, pseudoephedrine, ASA and other NSAIDs) during the first and second trimester. However, the results obtained in these studies may be affected by confusing factors. The sporadic reports of malformations in case reports are to be considered anecdotal because they do not have a specific pattern and have not been confirmed by subsequent epidemiological studies.
- *Second to third trimester*: it **is not recommended to take ASA after the 28th–30th week of pregnancy**, as ASA can lead to premature shrinkage or closure of the foetal arterial duct (resulting in pulmonary hypertension) and reduction of renal function (resulting in *oligohydramnios*). Intake near childbirth increases the risk of bleeding (including intracranial, gastrointestinal) in the foetus/infant, especially if premature. Due to the reduction in uterine contractility, ASA may prolong the duration of pregnancy and labour.
- *Breastfeeding*: **ASA intake is not recommended** as the medication passes into breast milk. In case of repeated maternal intakes, even at low doses, it can accumulate and cause toxic effects in the newborn due to reduced clearance.

Clopidogrel and Association of Several Anti-Platelets

At the moment, there are no studies that attest to the safety or toxicity of clopidogrel and the association of several antiplatelet agents (clopidogrel/ASA and ASA/dipyridamole) on the health of the foetus, when taken during pregnancy and during breastfeeding.

Anticoagulant Therapy

The use of anticoagulant treatment is very problematic as many anticoagulants cross the placental barrier.

Vitamin K Antagonists (Warfarin and Acenocoumarol)

Warfarin and acenocoumarol cross the placenta and are responsible for possible foetal diseases:

- **Warfarin: it is contraindicated in pregnant women or women** who may become pregnant because the drug crosses the placental barrier and can cause fatal bleeding of the foetus in the uterus, birth defects and abortion. Warfarin is not excreted in milk and **can be safely administered during breastfeeding**.
- **Acenocoumarol:** has a shorter half-life than warfarin (10–24 h), a faster effect on PT and a shorter duration of action (2 days). The daily dose is 1–8 mg daily.
- **Quarter I:** studies in the literature on the effects of the use of acenocoumarol and coumarols in general during the first trimester of pregnancy indicate an increase in the risk of congenital anomalies compared to expectations. The period of greatest sensitivity of the foetus is between the 6th and 12th weeks after conception. There are also reports of an increased risk of miscarriage.
- **Second to third trimester:** CNS and eye abnormalities have been reported when taking coumarols in the second to third trimester of pregnancy. The use of acenocoumarol and coumarols in general in the last period of pregnancy may induce slowed foetal growth, maternal and placental haemorrhage, foetal and neonatal brain microhaemorrhages and foetal loss.
- **Breastfeeding:** the drug passes into the breast milk where it is found at low concentrations. **There are no contraindications for breastfeeding during maternal therapy with acenocoumarol.** The control of the coagulation parameters of the newborn is indicated, and the indication for the administration of vitamin K should be evaluated with the paediatrician.

Fractional Heparin and Low Molecular Weight Heparins

Fractional heparin and low molecular weight heparins (EBPM) do not cross the placenta, and their possible fetopathic action has not been demonstrated until today.

Direct Opponents of Factor II and X (DOACs: Dabigatran, Rivaroxaban, Apixaban and Edoxaban)

At the moment, there are no studies in the literature that attest to the safety or toxicity of DOACs on health of the foetus, when taken during pregnancy and during breastfeeding [20].

Recanalization Therapy in Acute Ischemic Stroke

Fibrinolytic Treatment IV (t-PA)

T-PA has no teratogenic effects because it does not pass the placenta. However, in pregnant women, there is a potential risk of premature labour, placenta detachment or foetal death, although the clinical cases reported in the literature have most often been resolved in a positive manner. If there are no other absolute contraindications, thrombolytic therapy during pregnancy should be considered balancing the expected benefits against the potential risks to the foetus and the patient and should be discussed with the patient and/or family members.

Mechanical Thrombectomy

The treatment in these cases can be considered, after multidisciplinary evaluation, especially in the third trimester, even if there is no real shared guideline.

Some cases are reported in the literature where treatment has been successfully performed in pregnant patients, considering that the dose of radiation to the foetus has been evaluated on a case-by-case basis and considered acceptable according to ALARA indications, when performed. The angiographic thrombectomy procedure

involves an endovascular approach, possibly transradial, using low-dose fluoroscopic protocols if possible, with clot removal using thrombo-aspiration or stent-retriever catheters.

Table 16.5 summarises some useful pharmacological criticalities to be taken into account depending on the gestational period.

Fever Algorithm and Neurological Signs

A fever episode during pregnancy should be considered with particular attention: temperature over 38.0 °C during pregnancy should prompt the patient to seek immediate medical advice. The possible causes of hyperpyrexia and its consequences vary depending on the stage of pregnancy (trimester of pregnancy, labour or postnatal period) and may be due to infectious or noninfectious conditions. A fever may be associated with localized or systemic infections such as sepsis, connective tissue disorders (SLE, rheumatoid arthritis, Sjogren's syndrome, Behçet's disease), oncological diseases and haemolytic disease.

Early diagnosis in case of fever during pregnancy is mandatory because of the possible consequences for both the mother and the child.

Hyperthermia associated with neurological symptoms and/or neurological signs during pregnancy requires immediate multidisciplinary assessment/care in order to determine a timely diagnosis of potentially harmful/lethal conditions for the mother and child. Refer to the diagnostic algorithms presented in Chap. 6. We list below some conditions that must be considered in particular during pregnancy:

- **Haematological diseases.** Some conditions such as thrombotic microangiopathies may be characterized by fever and neurological signs. In particular (as previously mentioned) **thrombotic thrombocytopenic purpura** and **haemolytic uremic syndrome** have a higher incidence during pregnancy, even if they are not exclusive to this condition. Thrombotic thrombocytopenic purpura develops during the second trimester is characterized by the following clinical signs and symptoms:

Table 16.5 Pharmaco-metabolic criticalities typical of the management period

Medicine	Period		Breastfeeding
	Pregnancy	Puerperium	
rt-PA—tissue plasminogen activator	<i>Relative contraindication.</i> The benefit must be greater than the risk (level of evidence C), but the decision remains on a case-by-case basis	<i>Limited evidence.</i> Within 48 h of delivery increased risk of maternal foetal bleeding (level of evidence C)	<i>Limited evidence.</i> Recommended interruption transitory (level of evidence C)
Aspirin	<i>Safe up to 150 mg</i> in Q2 and Q3; no consensus in Q1 (level of evidence B)	<i>Interrupt the 36th week</i> or 1 week before childbirth (level of evidence C)	<i>Safe up to 150 mg</i> (on a type C basis)
Other antiplatelet agents (dipyridamole, ticagrelor, clopidogrel)	<i>Limited evidence.</i> Do not use (level of evidence C)	<i>Limited evidence.</i> Do not use (level of evidence C)	<i>Limited evidence.</i> Do not use (level of evidence C)
Heparin (LMWH (low molecular weight heparin), UFH non-fractionated heparin)	<i>Sure, sure, sure.</i> Preferable LMWH over UFH (level of evidence B)	<i>Stop 24 h before delivery</i> or as soon as possible in case of contractions or spontaneous rupture of membranes. Reintegration within 12–24 h after delivery (level of evidence B)	<i>Safe, not secreted in the milk</i> (level of evidence for UFH: A, for LMWH: B)
Vitamin K antagonists (warfarin, acenocoumarol)	<i>Contraindicated.</i> Teratogenicity, use LMWH/UFH especially in the first and third quarters (level of evidence B) In case of high cardioembolic risk (mechanical heart valves), use LMWH/UFH until the 13th week, then vitamin K antagonists until the end and then heparin (level of evidence A)	<i>Interrupt in the vicinity of childbirth</i> (in case of high embolic risk) and restart 1–3 days after delivery (level of evidence C)	<i>Safe</i> (level of evidence A)

Continued

Table 16.5 Continued

Medicine	Period		
	Pregnancy	Puerperium	Breastfeeding
Direct oral anticoagulants (DOAC) (apixaban, rivaroxaban, dabigatran)	<i>Limited evidence.</i> Do not use (level of evidence C)	<i>Limited evidence.</i> Do not use (level of evidence C)	<i>Limited evidence.</i> Do not use (level of evidence C)
Statins	<i>Limited evidence.</i> Do not use (level of evidence C) Non-essential therapy during pregnancy		<i>Limited evidence.</i> Do not use (level of evidence C)
Antihypertensive treatment (intravenous)	<p><i>Well tolerated and effective.</i> Labetalol, nifedipine and methyldopa (level of evidence A)</p> <p><i>Limited evidence.</i> Do not use atenolol, angiotensin receptor blockers and direct renin inhibitors (on a type C basis)</p>		
	<p><i>Sure, sure, sure</i> Compatible with breastfeeding—beta-blockers</p> <ul style="list-style-type: none"> – Calcium channel blockers – Methyldopa – ACE inhibitors <p><i>Limited evidence</i></p> <ul style="list-style-type: none"> – Diuretics <p>Do not use, may inhibit milk production (level of evidence C) (See LactMed)</p>		

Modified by van Alebeek et al. [18]

microangiopathic haemolytic anaemia, thrombocytopenia, **variable and fluctuating neurological signs and symptoms (from confusion to seizures and focal deficits)**, impaired renal function and **fever**. The clinical manifestations of haemolytic uremic syndrome are similar; this condition occurs in 90% of cases in post-partum (on average after 3 weeks). Clinically, neurological manifestations prevail in thrombotic thrombocytopenic purpura and renal manifestations in haemolytic uremic syndrome. The plasma exchange, if timely provided, has led to a significant improvement in the prognosis of patients with thrombotic thrombocytopenic purpura with remissions rate >75%, while the prognosis of haemolytic uremic syndrome in pregnancy as well as in sporadic adult cases not associated with pregnancy remains severe. As already mentioned, the differential diagnosis of these conditions with pre-eclampsia and HELLP syndrome is important, especially for prognosis and therapy. Unlike pre-eclampsia and HELLP syndrome, normal values of antithrombin are observed in thrombotic thrombocytopenic purpura and in uremic-haemolytic syndrome; moreover childbirth does not improve the prognosis and therefore has no therapeutic value.

- **Inflammatory/autoimmune diseases.** Pregnancy can lead to an **exacerbation of SLE**, usually of modest magnitude, more frequently **in the first two quarters**. Many drugs used to control SLE can be used during pregnancy; this applies to steroids, antimalarial drugs (e.g. hydroxychloroquine) and cyclosporine. Therefore, in case of history of connective tissue disease, it is possible that fever associated with neurological signs and symptoms may be a manifestation of exacerbation of the connective tissue disorder. Concerning Behçet's disease, it has been observed that pregnancy can exacerbate the neurological symptoms, while other recent retrospective analyses have concluded that the course of the disease seems to improve during pregnancy, especially in patients treated with colchicine, with no increase of pregnancy-related complications. In these cases, an accurate history and laboratory tests and neuroimaging are the cornerstones of the diagnostic workup. We recommend to consider **acute polyneuropathy of inflammatory demyelination** (AIDP or Guillain-Barré syndrome) in case of fever episode followed after few days by motor or sensory loss of the

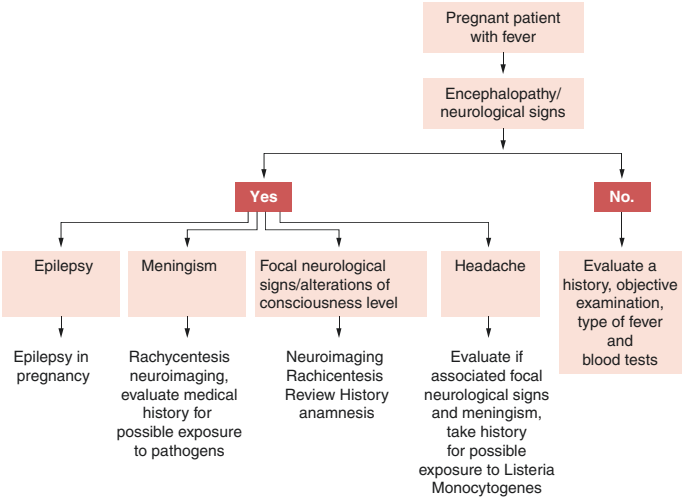
lower limbs. This condition is rarely seen in pregnancy. The clinical picture is typically characterized by motor disorder and progressive strength deficit of the lower limbs and hypo/areflexia.

- In some cases, the infection that caused the febrile episode is due to *Campylobacter jejuni* or to *Cytomegalovirus* (CMV).
- CMV infection is important to identify as it can confer a significant risk to the child through intrauterine transmission. The incidence of AIDP does not seem to increase during pregnancy but rather in the period immediately after childbirth, as it is the case in patients with multiple sclerosis.
- If Guillain-Barré syndrome is suspected, a CSF test may be necessary to assess the presence of the typical albuminocytological dissociation: high level of proteins in a noninflammatory sample. Lumbar puncture can be performed safely even during pregnancy. Neurophysiological studies show demyelinating polyneuropathy. However, both CSF and electroneurography can be normal in a small percentage of AIDP patients. Treatment of Guillain-Barré syndrome with plasmapheresis and/or IV immunoglobulin is indicated even during pregnancy. Guillain-Barré syndrome does not seem to affect the uterine contractile activity, and therefore the child delivery should be based upon obstetrical indicators. However, it is recommended to ensure that these patients have an anaesthetist during childbirth; the use of succinylcholine is not recommended. If there is a suspect for demyelinating diseases (such as multiple sclerosis), MRI is indicated.
- **Infectious diseases.** The presence of headache, fever and neurological symptoms/signs such as papilloedema, visual disorders, lethargy and mental confusion requires immediate attention and evaluation in order to identify any infectious conditions that may occur during pregnancy [1]. **Bacterial meningitis** during pregnancy is a rather rare and extremely serious condition associated with high risk of mortality for both mother and child [21]. Clinical presentation is typical with high fever, headache, altered mental state and nuchal rigidity.
- Infections of the ear and/or mastoid are risk factors for meningitis; there are not specific pathogens associated with the risk of meningitis in pregnancy with the exception of *Listeria monocytogenes*, a gram-positive bacterium, widely spread in

the environment, with an intracellular tropism. It is found in 2–13% of food samples (minced meat, smoked fish, cheese and cold cuts). Pregnant women have a 12-fold increased risk of developing a *Listeria* infection compared to healthy adults, due to decreased cellular immunity. In two-thirds of cases, the infection develops during the third trimester, and it presents as a flu syndrome. The diagnosis is based on blood cultures, and testing for *Listeria* should be clearly specified.

- If the infection is confirmed, emergency treatment is required during pregnancy, an early surgical delivery or termination of pregnancy should be evaluated as the foetal impairment is severe and perinatal mortality reaches 25–50% of cases. During pregnancy, the recommended dosage of ampicillin for listeriosis is 2 g every 6–8 h. This dosage allows appropriate intracellular infiltration and placenta barrier-crossing. The optimal duration of therapy during pregnancy has not been established, but 3–4 weeks of treatment are considered as a minimum period [21] (Fig. 16.5).

Figure 16.5 **Fever algorithm and neurological signs**



Therapeutic Approach

Antibiotic Therapy [21] (Table 16.6). Bacterial meningitis during pregnancy is an uncommon disease, with significant maternal and child mortality, and therefore requires intensive and multidisciplinary management in an appropriate environment. Pathogens other than *S. pneumoniae* and *L. monocytogenes* causing bacterial meningitis during pregnancy are rare and are reported only in isolated cases. The choice of initial antibacterial therapy is based on epidemiological data, on the age of the patient, clinical picture and antibiogram.

Combination therapy with vancomycin and a third-generation cephalosporin (ceftriaxone or cefotaxime) has become the standard approach to empirical antimicrobial therapy in bacterial meningitis. Dexamethasone associated or not with the first dose of antibiotics has been shown to reduce the risk of death and neurological disability in adults with pneumococcal meningitis.

The following antibiotics should be avoided as they are potentially harmful to children: chloramphenicol, ciprofloxacin, kanamycin, streptomycin, gentamicin, nitrofurantoin, tetracycline and sulphonamides.

Patients with listeriosis without abnormalities of cerebrospinal fluid can be treated for 2 weeks; meningitis should be treated for

Table 16.6 In case of severe *Listeria monocytogenes* infection

Antibiotic	Adult dose
Ampicillin	2 g/dose IV, every 4 h
Gentamicin	1–2 mg/kg/dose IV, every 8 h (monitor plasma levels)
Trimethoprim-sulfamethoxazole	5 mg TMP/kg/dose IV (max 160 mg TMP), every 6 h
Penicillin G	4 million units IV, every 4 h

To note:

- Trimethoprim-sulfamethoxazole is contraindicated in the first trimester of pregnancy and during the ninth month. It is also contraindicated in infants under 8 weeks of age.
- Cephalosporin is ineffective in case of *L. monocytogenes* infection.
- Patients with listeriosis do not need isolation.

3 weeks; and relapses have been documented with shorter durations of therapy. Prolonged therapy beyond 3 weeks may be necessary in case of encephalitis, cerebral abscess and endocarditis and must be considered in any case in an immunocompromised person.

Multiple Sclerosis Algorithm

Multiple sclerosis (MS) is the most common chronic inflammatory, demyelinating, neurodegenerative and immuno-mediated disease of the central nervous system (CNS); it commonly affects young women of childbearing age and is the leading cause of chronic disability in young adults.

Approximately 80% of MS patients are affected by the relapsing-remitting form (RRMS), characterized by unpredictable relapses lasting at least 24 h, followed by prolonged periods of remission (partial or total) without disease progression.

A variable proportion of 30–50% of patients with RRMS experience a severe form of progressive secondary MS (SPMS), characterized by progressive neurological degeneration, with or without overlapping relapses, and an increasing burden of disability. A minority of patients suffer from severe forms of primary progressive MS (PPMS) or recurrent MS (PRMS), characterized by a progressive worsening of the disease from onset, regardless of relapses. The clinical course is variable and unpredictable.

There is increasing evidence that the disease has no direct impact on fertility and that pregnancy does not affect long-term disability. Appropriate *counseling by* health professionals, in particular neurologists, is absolutely necessary to ensure that patients are properly informed. Disease management is also complicated by the number of available treatment options, their potential teratogenic effect and treatment management in pregnancy.

The neurologist working in the emergency-urgency setting must be able to answer the questions of a patient with MS who discovers to be pregnant. In many centres there are dedicated clinical pathways, but urgent advice may be needed.

On the other hand, the emergency neurologist must be able to manage any complications/recurrence of the disease together with gynaecology/obstetrics specialists with a multidisciplinary approach. Table 16.7 summarises the possible criticalities/questions related to the time: before and during pregnancy, childbirth and puerperium.

Disease Progression and Relapse Management

The frequency of relapses decreases during pregnancy and increases during puerperium; the frequency pattern of relapses usually returns to pre-pregnancy levels within 6 months after delivery [23–25].

Patients with relapses during pregnancy may benefit from corticosteroid therapy. The safety of steroid use varies depending on the type and dose of the chosen steroid, the period of pregnancy during which it is administered and the duration of administration (Fig. 16.6).

Therapeutic Approach

Patients with multiple sclerosis may benefit from a short cycle of prednisolone or methylprednisolone (3–5 days). This therapy can be safely administered during the second and third trimester of pregnancy; methylprednisolone and prednisolone are actively metabolized by the placenta and reach a low concentration in the foetal blood (less than 10% of the maternal dose) This minimize the risk of affecting foetal growth that seems associated with the use of dexamethasone or betamethasone in longer cycles [26, 27]. Betamethasone and dexamethasone pass through the placenta, undergoing only minimal metabolism and reaching an almost integral dose of the foetal circulation. If possible, it is recommended to avoid the use of steroids during the first trimester of pregnancy in relation to the risk, albeit rare, of teratogenic effects such as cleft palate and harelip. In this phase of gestation, steroids should be limited to severe exacerbations only.

Table 16.7 Criticality/questions related to the time: before and during pregnancy, childbirth and puerperium

Question/critical issues	Current evidence, before pregnancy
Fertility and child development	In general, there are no evidences of an association between maternal MS and adverse effects on child development. The effect of MS on fertility is uncertain: hormonal abnormalities have been observed in female patients with MS that may have an impact on fertility, but the evidences are still limited
Assisted reproduction/in vitro fertilization	The use of agonists and antagonists of the gonadotropin-releasing hormone (GnRH) may be associated with a temporary increase in the risk of relapse. The use of GnRH antagonists seem to be less risky than GnRH agonists. The choice must be agreed upon a multidisciplinary consultation
Oral contraceptives	The use of oral contraceptives is not associated with an increased risk of relapse in MS. Long-acting reversible methods of contraception (LARCs) are particularly effective birth control methods because they reduce the need for patient compliance
Disease-modifying therapies (DMTs) and need of <i>washout</i> during the period of conception	It depends on the therapy; there is no need to suspend the medication in the period before pregnancy for glatiramer acetate (GA), interferon-B (IFNb) and natalizumab
Question/critical issues	Current evidence during pregnancy
Impact of pregnancy on MS prognosis	Pregnancy is associated with a reduction in disease activity during the third trimester, followed by an increase in the post-partum period. No long-term negative impact on disability
Impact of MS on the outcome of pregnancy	No increase in ectopic pregnancies, birth defects, miscarriages or perinatal mortality

Continued

Table 16.7 Continued

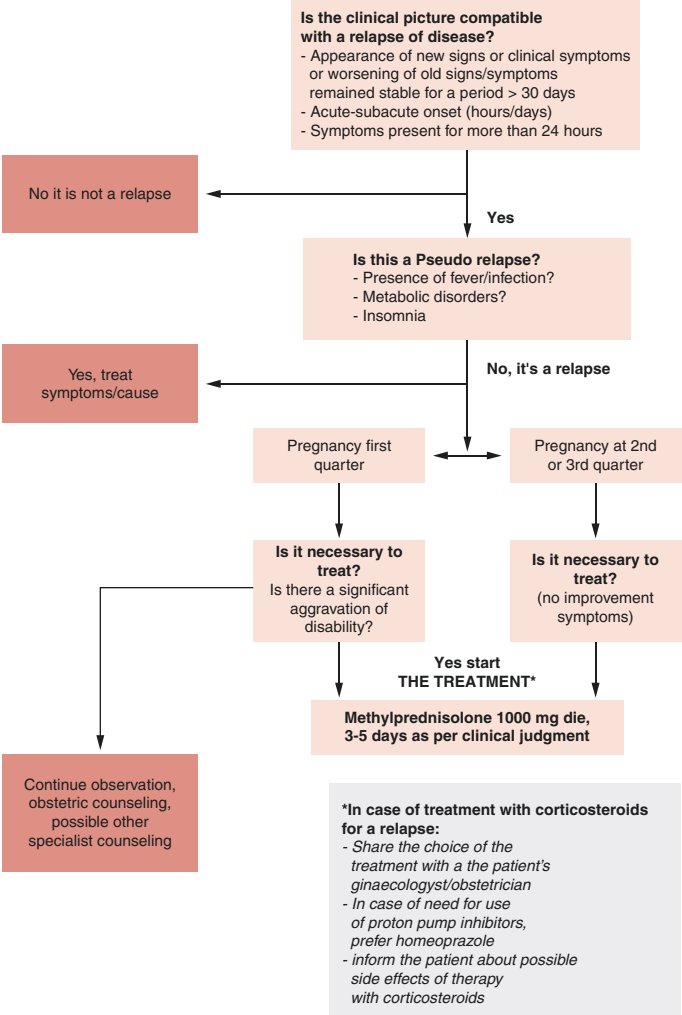
Treatment with DMTs during pregnancy	In general, DMTs are not used during pregnancy. Symptomatic treatment is allowed only for short periods, when appropriate and necessary. Glucocorticoids can be used for possible relapses at any time during pregnancy. Magnetic resonance imaging (MRI) can be performed in selected cases by assessing risks/benefits and avoiding the use of contrast, unless absolutely necessary
Question/critical issues	Current evidence, childbirth and puerperium
Screening, childbirth and obstetric analgesia/anaesthesia	The use and possible choice of analgesia/ anaesthesia techniques should be based exclusively on obstetrical decisions/assessments. Any type of analgesia during delivery is acceptable, as long as there is an indication from the gynaecologist specialist; epidural and spinal anaesthesia can be used safely and have no impact on disability or activity of the disease
Breastfeeding	There are no evidence concerning of DMTs secretion in breast milk and possible adverse effects in the newborn. Since in patients with a more active disease a rapid resumption of DMTs after childbirth may be appropriate, suspension of treatment in patients at high risk of disability progression may be considered
Disease activities	The first 3–6 months after delivery are a period of high risk for increased clinical and neuroradiological activity of disease

Modified by Coyle et al. [22]

In a general sense, medications used for the symptomatic treatment of MS during pregnancy (e.g. analgesics, spasticity treatment options and antidepressants) should be carefully evaluated and used at the lowest effective dose, for the shortest possible time.

MS does not affect physiological pregnancy, nor it leads to a high-risk pregnancy for itself, and, therefore, unless indicated by a gynaecologist/obstetrician, preventive hospitalization is not necessary.

Figure 16.6 Multiple sclerosis algorithm



Algorithm of Delirium and Pregnancy Psychosis

Early diagnosis and treatment of psychiatric disorders during pregnancy may prevent post-partum morbidity, thus limiting the risks for the mother and child. Both psychotherapy and pharmacotherapy should be considered. The occurrence of frank psychotic episodes in pregnancy is rather rare, however, in women with a history of psychosis (bipolar disorder, psychotic depression, schizophrenia), particularly psychosis occurred during previous pregnancies, the rates of relapse are high [28].

Neuropsychiatric symptoms can complicate some conditions that develop during pregnancy. This is the case of eclampsia where psychiatric symptoms may occur, particularly visual hallucinations. The mechanism by which these disorders occur has been attributed to cortical damage of the occipital cortex. Recently cases of patients with pre-eclampsia who also reported visual hallucinations have been described.

The psychotic disorder in a patient with no history of psychiatric illness and drug abuse could be the manifestation of non-convulsive illness. These are quite rare conditions, but as described in some cases in the literature, hormonal changes related to pregnancy may be a possible explanation for the outbreak of an epileptic syndrome. Non-convulsive epileptic disease can produce a wide spectrum of clinical symptoms depending on the regions and relative area of the brain that is rendered dysfunctional by persistent epileptic discharges. Non-convulsive state may determine a clinical picture similar to psychosis. In this case, a complete diagnostic procedure is required: EEG, possibly brain MRI.

For further information please refer to Chap. 4.

In case of sudden changes of the mental status and onset of neurovegetative disorders and neuromuscular hyperactivity, if the patient is on therapy with SSRI, the **serotonergic syndrome should be considered**. This potentially lethal condition is triggered by taking two or more drugs that increase the level of

serotonin, resulting in suppression of the synthesis or release of the natural neurotransmitter itself. The incidence of serotonergic syndrome is progressively increasing due to the increased prevalence of serotonergic prescription drugs. In obstetrics, substances such as fentanyl, granisetron, hydrocodone, meperidine, metoclopramide, ondansetron and oxycodone are commonly used in labour and during childbirth; these drugs can contribute to the onset of serotonergic syndrome of certain risk factors such as tricyclic therapy and SSRI but also antipsychotics and pain killers are present. Pregnancy for some characteristics could be a risk.

The therapy of this serious condition involves the elimination of all serotonergic agents, supportive therapy until the symptoms are resolved; this happens in about 24–72 h in 60% of cases. The time period depends on the half-life of the drug.

Support actions may include:

- Oxygen administration.
- IV fluids.
- Cardiac monitoring.
- Airway intubation.
- Moderate to severe serotonergic syndrome may require sedation with benzodiazepines.
- Administration of serotonin antagonists as an antidote, such as cyproheptadine.

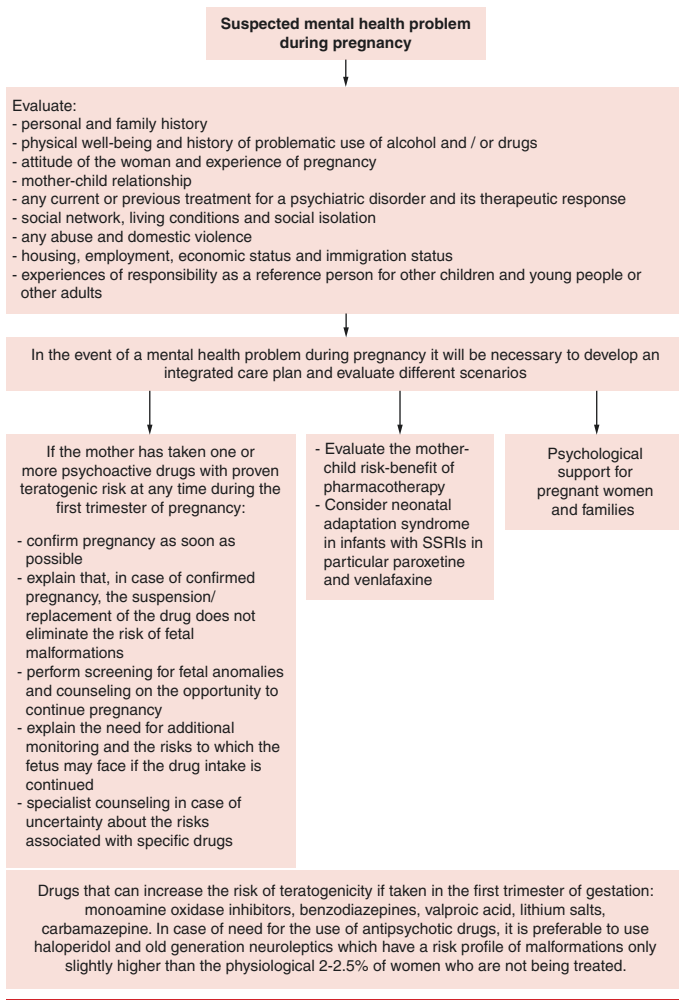
The algorithm on delirium and pregnancy psychosis is shown in Fig. 16.7.

Therapeutic Approach [29]

Therapy of Psychotic Disorders

Even if pregnancy should be considered a physiological event in a woman's life, in patients suffering from psychiatric disorders, hormonal fluctuations, changes in body structure, working difficulties, stress and poor adherence to pharmacological therapies can worsen the pre-existing pathology and determine a significant increase in the risk of maternal, foetal and neonatal complications.

Figure 16.7 Algorithm delirium and pregnancy psychosis



The management of pregnant women with psychotic disorders is complex and requires a multidisciplinary approach and coordination between different specialists (psychiatrist, gynaecologist, teratologist, geneticist, neonatologist, paediatrician).

The treatment of psychotic disorders is based on drug therapy and psychotherapy. The antipsychotic drugs used act mainly through antagonistic action on dopaminergic receptors D2 [29].

During pregnancy, an untreated or ineffectively treated psychotic condition can have significant psychological and physical repercussions on the mother, child and family. Therefore, careful clinical monitoring is necessary to prevent or diagnose early relapses of the maternal pathology, especially in the postnatal period and in the first year of life of the newborn.

The following recommendation should be considered:

- Plan pregnancy by informing the woman/couple of possible maternal and obstetrical complications and possible embryo-foetal risks (even at a distance) related to maternal pathology and medication during pregnancy.
- Inform the patient about the risks associated with inadequate psychiatric therapy during pregnancy.
- Take adequate folic acid supplementation at least 1–3 months before and during pregnancy.
- Don't smoke.
- Refrain from taking substances such as drugs and alcohol.
- Continue therapy during pregnancy to contain maternal disease (both in the case of planned and unplanned pregnancy).
- Constantly monitor drug therapy because pregnancy determines significant changes in the pharmacokinetics of drugs (absorption, distribution and elimination) with consequent changes in their plasma concentration, which are sometimes clinically relevant.
- Promote models of control, psychosocial support and monitoring of the disease with the woman and her family.
- Promote careful obstetric monitoring (including second-level obstetrical ultrasound) when using antipsychotic drugs.

- Monitor weight and glucose and lipid metabolism, particularly when using second-generation antipsychotic drugs.
- Plan the birth and carry out a short- and long-term clinical follow-up of the newborn-child.

Pharmacological Therapy in Pregnancy [29]

Different types of drugs are available, administered in mono or polytherapy, depending on the severity of the disease and the effectiveness of the therapy itself. In general it is advisable to:

- Prescribe the most effective medication for the patient and with the lowest maternal-foetal risks.
- Choose the medications on which you have the greatest clinical experience (e.g. for the longest time on the market) and at the lowest effective dosage.
- Take the medication in monotherapy.

Today, data on the safety of second-generation antipsychotics have exceeded those on old -generation antipsychotics.

First-generation antipsychotic drugs:

- Haloperidol (it is the first-generation drug for which there are more safety data).
- Chlorpromazine.

Second-generation antipsychotic drugs:

- Quetiapine (poor placental passage)
- Clozapine
- Olanzapine
- Risperidone (slight increase in malformative risk)

Benzodiazepines **are indicated** in combination with antipsychotic drugs.

Attention, please:

- During pregnancy, adequate monitoring of drug therapy is necessary due to changes in pharmacokinetics.
- The risk of gestational diabetes and low birthweight can be increased by second-generation antipsychotics.

Drug Therapy During Breastfeeding

Caution: Clozapine is contraindicated during breastfeeding due to the increased risk of agranulocytosis and seizures [30].

Many first-generation antipsychotics (haloperidol, perphenazine, chlorpromazine) are excreted in breast milk in small amounts (relative infant dose, RID <10%) [31]. Among the second-generation antipsychotics, the amount excreted in breast milk is:

- Low for olanzapine and quetiapine
- Moderate for risperidone and aripiprazole
- High for amisulpride

No serious adverse events have been reported [30]. Drowsiness, irritability, motor abnormalities and difficulty sucking after exposure to these drugs are reported, and infants should be closely monitored, especially if premature or with low birth weight. Cases of developmental delay in infants exposed to antipsychotics with breastfeeding are also reported, while there is little data on long-term neurocognitive outcomes [29].

Neuromuscular Diseases Algorithm

The physiological changes of pregnancy, labour, delivery and puerperium increase the risk of neuromuscular complications. Acquired compression neuropathy and radiculopathy may occur during pregnancy and delivery. Inflammatory nerve diseases and neuromuscular junction diseases put both mother and foetus at risk when they occur during pregnancy [32, 33].

Acquired Compressive Nerve and Root Disorders During Pregnancy and Puerperium

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is the most frequent compression neuropathy in pregnancy (incidence of 2–35% in pregnant women) [34]. CTS occurs most frequently in the third trimester and may be

due to fluid retention. Usually symptoms of CTS improve after delivery, and surgery is not necessary, even if the data on the postpartum course are conflicting [35]. Symptoms may also arise during lactation.

Lower-Limb Neuropathies and Lumbosacral Radiculopathies

The incidence of these forms varies between 0.11% and 0.98%. Lateral femoral cutaneous syndrome (meralgia paresthetica), femoral neuropathy, obturator neuropathy, sciatic neuropathy, peroneal neuropathy and injuries to the lumbar and sacral plexus may be secondary to anatomical changes induced by pregnancy, positioning in labour, assisted delivery (i.e. use of forceps) or caesarean section. Low back pain without neurological signs is a frequent problem in pregnancy, while radiculopathies due to lumbar disk herniation are rare, usually affecting L5 or S1 roots and are most often treated conservatively [33].

Other Neuropathies

Bell's Palsy

Bell's palsy (peripheral facial nerve paralysis) is more common in the third trimester and the early puerperium. Bell's palsy has been significantly associated with obesity, hypertension and pre-eclampsia. The prognosis in pregnant women is uncertain. Some authors report excellent recovery even without treatment (the production of endogenous steroids in the pregnant woman may influence recovery) [33], while others report a worse prognosis than nonpregnant women despite steroid treatment [36].

Intercostal Neuralgia and Radial Neuropathy

Intercostal neuralgia or thoraconeuralgia gravidarum is characterized by pain and numbness in the distribution of a thoracic root or intercostal nerve. Symptoms typically resolve after delivery [37].

Both hereditary neuralgic amyotrophy and neuralgic amyotrophy have been reported in pregnancy and have good prognosis for spontaneous recovery, although they may recur in subsequent pregnancies.

Bilateral radial neuropathies may be due to nerve compression at the humeral spiral groove in patients using birthing bars for upright positioning during labour.

Inflammatory Neuropathies

Guillain-Barré Syndrome

Although an increased risk of Guillain-Barré syndrome (GBS) is described in the first 14 days after delivery, the incidence of this disease in pregnancy does not seem different from that of the general population [38]. GBS is often triggered by infections, particularly *Campylobacter jejuni* or *Cytomegalovirus* (CMV) infections. The latter is particularly important in pregnancy because congenital *Cytomegalovirus* (CMV) infection can cause severe adverse neonatal outcomes.

Chronic Inflammatory Demyelinating Polyneuropathy and Multifocal Motor Neuropathy

Chronic inflammatory polyneuropathy (CIDP) is rare in women of childbearing age. Unlike GBS, where the course and severity of the disease are not affected by pregnancy, CIDP can worsen during pregnancy. Relapses in patients with a previous history of CIDP are more frequent in the third trimester or in the immediate postpartum period.

Neuromuscular Junction Disorders

Myasthenia Gravis

Female incidence of myasthenia gravis (MG) peaks in the second and the third decade and therefore coincides with family planning and fertility [39]. Issues related to the care of patients with MG in the childbearing age may include questions about fertility, pregnancy planning, drug safety and treatment optimization preceding conception. Long-term outcome of MG is not affected by pregnancy. During pregnancy, frequent monitoring of symptoms and sometimes therapeutic adjustment is required.

The course of MG during pregnancy is unpredictable and highly variable and does not appear to be influenced by the severity of the symptoms before conception or by the course of the disease during previous pregnancies [40]. One-third of women experience a worsening of their symptoms, usually during the first trimester or after delivery. Improvement in symptoms or complete remission usually observed in the second and third trimester seems to be related to the physiological immunosuppression induced by high levels of alpha-fetoprotein (AFP). Instead, the abrupt reduction of AFP after delivery may partly justify the clinical deterioration [41].

Respiratory function should be carefully monitored as enlargement of the uterus may limit the range of the diaphragm.

- **Onset in pregnancy or post-partum.** MG may begin in pregnancy (12–15% of mothers with MG) or in post-partum [42]. Changes in the immune system (production of oestrogen-induced cytokines or immunoglobulins, drop in AFP levels) stress and sleep deprivation are all possible triggers. In some cases the onset may be represented by a myasthenic crisis.
- **Influence of MG on pregnancy.** Women with MG do not have an increased risk of miscarriage, premature birth and intrauterine growth retardation [43].
- **Birth and post-partum.** In women with MG, natural delivery should be encouraged, while caesarean section should be practiced only on the basis of obstetrical indications. MG does not affect the smooth muscles of the myometrium, although fatigue can affect the second phase of labour, during which the skeletal muscle is involved in voluntary effort. In this phase of labour, cholinesterase inhibitors may be used, including intravenous cholinesterase. Epidural anaesthesia (or combined spinal-epidural anaesthesia) is recommended in vaginal delivery, while regional anaesthesia is recommended in caesarean section. General anaesthesia and neuromuscular blockers should be avoided if possible [32].
- **Transient neonatal myasthenia.** Transplacental passage of antibodies causes transient neonatal myasthenia which manifests itself with diffuse hypotonia, poor sucking, weak crying

and respiratory difficulty. The incidence of transient neonatal myasthenia (not to be confused with congenital myasthenia) varies between 10% and 30% of newborns born to mothers with MG [40, 44].

Botulism

Symptoms that should give rise to the suspicion of botulism in pregnant women are nausea, vomiting, diplopia, dry mouth, lethargy, dyspnoea, drowsiness, fixed mydriasis, muscle weakness and respiratory failure. Diagnosis should be based on clinical evaluation and objective examination and confirmed by laboratory tests and electromyography. MRI without gadolinium (or in emergency cases also CT) can be useful in differential diagnosis with stroke. Differential diagnoses include GBS, myasthenia and opioid overdose.

Tetanus

It is an intoxication caused by the exotoxin (tetanospasmin) produced by *Clostridium tetani*, a gram-positive anaerobic bacterium. It starts with tonic spasms of the skeletal muscles and is followed by paroxysmal contractions. The muscle stiffness initially involves the jaw (lockjaw) and neck and later becomes generalized. It can be associated with autonomic dysfunction. Tetanus is still an important cause of maternal and neonatal morbidity and mortality, especially in developing countries.

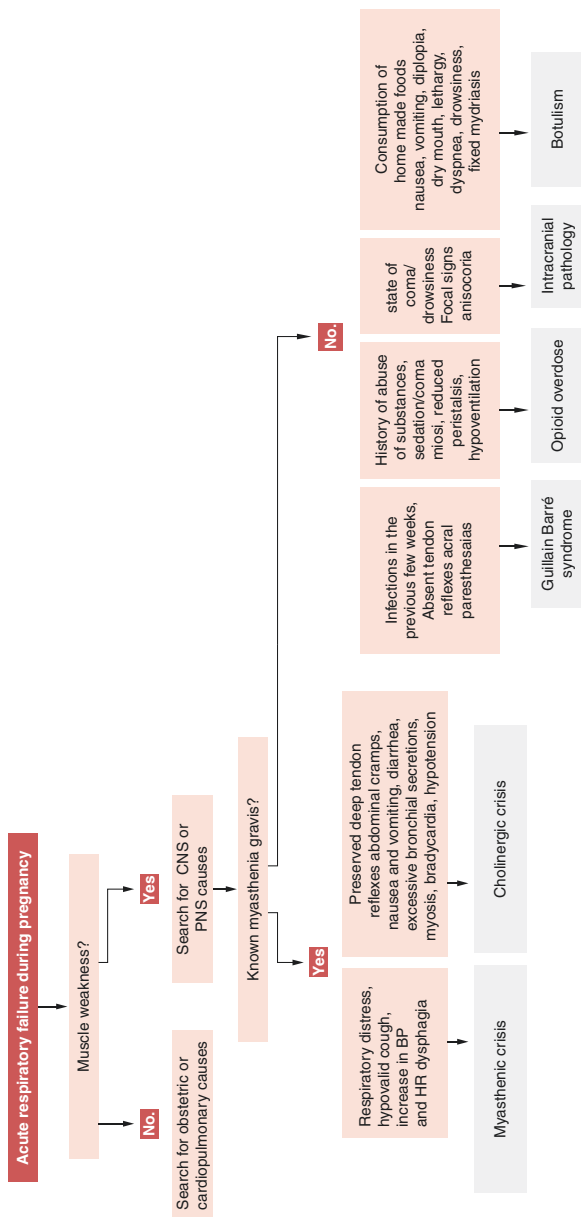
Respiratory Failure in Pregnancy (Fig. 16.8)

Therapeutic Approach

Carpal Tunnel Syndrome

The treatment is conservative and involves the use of braces, physical therapies and a low-salt diet; in case of failure, steroid injections into the carpal tunnel are useful.

Figure 16.8 Decision tree acute respiratory failure in pregnancy



Lower-Limb Neuropathies and Lumbosacral Radiculopathies

When pharmacological treatment is required, paracetamol and local treatments such as lidocaine patches (category B according to FDA) should be favoured, while neuropathic pain medications (antiepileptics and tricyclic antidepressants) should be avoided and NSAIDs should be used with caution for the risk of abortion or malformations. Braces can be useful in foot drop.

Paralysis of Bell

The use of prednisone (category C according to FDA) is controversial, and a conservative approach may be preferable. With regard to antivirals (acyclovir and valacyclovir), retrospective data suggest that these drugs are not associated with major malformations, but the benefit is uncertain.

Guillain-Barré Syndrome

The treatment of GBS in pregnancy involves the use of immunoglobulins IV or plasmapheresis (PEX). PEX may alter plasma volume producing hypotension, while IVIg may increase the risk of thromboembolism and IgA nephropathy.

Supporting therapy is also essential, including prevention of deep vein thrombosis and close monitoring of respiratory and cardiac function. The threshold for intubation to prevent hypoxemia that could damage the foetus may be lower.

In the largest study of pregnant women with GBS, 35% of them had preterm delivery, most often due to labour induced by worsening neurological conditions of the mother. The caesarean section should be chosen on the basis of obstetrical indications [45].

Chronic Inflammatory Demyelinating Polyneuropathy and Multifocal Motor Neuropathy

IVIg and PEX are used in the treatment, as in GBS, as well as oral or IV steroids (prednisone, methylprednisolone), which do not play a role in GBS therapy. CIDP does not appear to have a negative impact on the child [46]. Motor neuropathy with conduction blocks

(MMN) may worsen during pregnancy and may require treatment with IVIg [47].

Myasthenia Gravis

Treatment of MG in Pregnancy

The treatment of choice of MG in pregnancy is represented by pyridostigmine and corticosteroids [48, 49].

Pyridostigmine may be sufficient to control symptoms in patients with mild manifestations or exclusively ocular symptoms. Doses up to 600 mg/day were found to be safe for the foetus.

In patients requiring immunosuppressive therapy, corticosteroids (prednisone) are the treatment of choice in pregnancy because of the low teratogenic risk (while some retrospective studies indicated an increased risk of cleft palate with the use of corticosteroids in the first trimester, recent studies seem not to confirm this association) [50]. High doses of steroids were however associated with premature membrane rupture and gestational diabetes.

Immunoglobulins (IVIg) are used to treat patients who do not respond to pyridostigmine and corticosteroids and in myasthenic crises. The safety of IVIg during pregnancy is well-documented [51], although some side effects such as hyperviscosity or volume overload may become relevant during pregnancy.

Plasmapheresis (PEX) has been successfully used in pregnant patients with MG or other conditions [52], although there is evidence of an increased risk of premature delivery, infection or bleeding (probably due to the removal of hormones, immunoglobulins and coagulation factors).

Azathioprine has been shown to be teratogenic in animals, but clinical experience in organ transplant patients is reassuring [53]. However, azathioprine has been associated with intrauterine growth retardation and preterm delivery.

Cyclosporine has also been associated with intrauterine growth retardation, although no teratogenic effects have been reported in humans.

Mycophenolate mofetil has been associated with first trimester abortion and various congenital malformations (cleft lip, ear, palate, limb, oesophagus, kidney and CNS malformations) [53].

Methotrexate was also found to be teratogenic and was associated with an increased risk of abortion [53].

Finally, the data on the use of rituximab in pregnancy are uncertain.

Treatment of MG During Breastfeeding

With a maternal steroid dose of less than 20 mg/day, the drug levels in milk remain low, and these levels are not associated with adverse effects on the newborn. Breastfeeding while taking azathioprine or cyclosporine is considered safe. Some authors suggest that breastfeeding should be avoided at the peak serum concentration. There are no data on the use of mycophenolate or rituximab during lactation [54] (Table 16.8).

Botulism

The treatment involves the early administration of antitoxin, regardless of gestational age. Sometimes a support therapy with mechanical ventilation in intensive care is required [55].

Tetanus

The treatment of pregnant women does not differ from that of nonpregnant patients and includes the prevention of further toxin absorption, wound debridement, antibiotic therapy and supportive therapy. Tetanus toxoid vaccine can be administered during pregnancy [56].

Table 16.8 Recommendations on drug treatment and safety in patients with MG before, during and after pregnancy [48]

Medicine	Period		
	Before conception	Pregnancy	Breastfeeding
Treatment of choice			
Pyridostigmine	No limitation	<600 mg/day	High doses can cause gastrointestinal disturbances in the newborn
Corticosteroids (prednisone)	No limitation	Lowest effective dose	No limitation
Treatment of myasthenic crises			
IVIg	No limitation	Treatment of choice	No limitation
PEX	No limitation	Monitor fluid movements	No limitation
Treatments that can be continued (not recommended to start during pregnancy)			
Cyclosporine	Recommended contraception	Continuation of the therapy can be considered	It can be considered
Azathioprine	Recommended contraception	Continuation of the therapy can be considered	Considered acceptable by experts
Contraindicated treatments			
Methotrexate	Recommended contraception up to 3 months after the suspension	Contraindicated	Contraindicated
Mycophenolate mofetil	Recommended contraception up to 6 weeks after suspension	Recommended interruption	Not recommended (no data)
Treatments at unknown risk			
Rituximab	Not recommended for lack of data	Not recommended for lack of data	Not recommended for lack of data

Algorithm on Dizzying Syndromes

Dizziness and fainting are quite common disorders in pregnancy, in most cases, these are pre-syncope episodes, with imbalance (*dizziness*) and episodes of visual blurring (Chap. 8 for definitions and differential diagnosis), which depend on the slight drop in pressure during pregnancy related to the dilation of blood vessels due to hormonal changes and the passage of part of the blood to the child. Therefore, although the approach to the dizzy pregnant or postnatal patient does not differ from the approach to the generic dizzy patient, it must take into account the importance of differential diagnosis with pseudo-vertigo with particular reference to symptomatic arterial hypotension linked to the pregnancy condition (Chap. 8).

In addition, it is sometimes difficult to distinguish attacks of dizziness from attacks of nausea and vomiting, which are quite common, especially in the first trimester of pregnancy. In these cases, checking for the presence of nystagmus may help in differential diagnosis (see the vertigo algorithm in the dedicated chapter).

Therapeutic Approach

Traditionally, doctors are quite reluctant to prescribe antiemetics, especially during the first trimester, unless you have to treat hyperemesis in pregnancy. However, many drugs are safe and effective for antiemetic use. H1 antihistamines, which are very effective in patients with vestibular nausea, can be administered during vertigo episodes.

Available data suggest that meclizine and dimenhydrinate are the antiemetics with the lowest risk of teratogenicity.

When vomiting is continuous, metoclopramide could also be considered IV.

There are not enough safety evidences to recommend ondansetron as antiemetic during pregnancy.

Among the most recent drugs, pyridoxine (vitamin B6) appears to be effective in reducing the severity of nausea in the first trimester of pregnancy, without evidence of teratogenicity. Zenzer/ginger is used to prevent motion sickness.

On the contrary, the use of betahistine, widely prescribed and used by doctors for vertigo, is contraindicated during pregnancy. Liberation manoeuvres and vestibular exercises can be performed on pregnant patients with paroxysmal positional vertigo. There is little data on the course of Menière's disease during pregnancy.

Although diuretics should be avoided during pregnancy, they can be administered as maintenance therapy in the first trimester in reduced doses. However, their administration beyond the 12th week is no longer recommended, due to possible hypothermia, hyperbilirubinemia, thrombocytopenia and placental hypoperfusion. Therefore, it seems that the combination of dimenhydrinate and vitamin B6 is safer during recurrences of Menière's disease.

Diagnostic Tests and Radiation Protection During Pregnancy

The diagnostic tools available to the neuroradiology use ionizing radiation (conventional radiology, CT and procedures in scopia), radio frequencies (magnetic resonance imaging) and ultrasound (ultrasound). There are no specific indications for patients undergoing neuroradiological examinations during pregnancy, so we refer to the radiological standard. The legislation published in the Official Gazette, whose reference is Legislative Decree 187 of 26/5/2000, deals in general with radiation protection during pregnancy and breastfeeding [57].

The key point is that at the time of the diagnostic investigation or treatment, the prescribing physician together with the neurologist must collect a precise medical history of the female patient, including whether or not she is pregnant.

In cases where pregnancy cannot be excluded, the specialist must consider the dose that will result to the uterus as a result of the examination.

If the estimated dose is greater than 1 mSv, it will be necessary to refer to the ALARA (as low as reasonably achievable) principle, with particular attention to the principle of justification, necessity or urgency of the examination, considering possible alternatives or procrastination of the examination or treatment.

The basic principles of radioprotection (ALARA) are: [57]

- **Justification:** Exposure to ionizing radiation must be justified in advance and periodically reviewed in the light of the benefits arising from them.
- **Optimization:** Exposure to ionizing radiation has to be kept “as low as reasonably achievable” taking into account also economic and social factors.
- **Dose limitation:** The sum of the doses received and administered must remain into certain limits.

With reference to Annex 187 on specific provisions for exposure during pregnancy, where pregnancy is certain, exposure to embryo and foetus rays is possible but only in cases of established need or urgency [57].

Therefore, when it is not possible to postpone the investigation or treatment, the specialist must inform the woman of the possible risks to the foetus from exposure to ionizing or electromagnetic radiation or ultrasound, depending on the examination prescribed.

Ionizing Radiation

Cells that reproduce most rapidly and eutrophic cells are the most sensitive to radiation, and cell sensitivity increases depending on the stage of cell division. Cells in the process of formation are more radiosensitive and thus can be damaged more easily than the mature ones. Therefore, when it is not possible to postpone the investigation or treatment, the physician must inform the woman of the possible risks to the foetus from exposure to ionizing or

electromagnetic radiation or ultrasound, depending on the examination to which she will undergo.

Two types of possible effects should be evaluated [58–61]:

- **Deterministic effects:** these are collateral effects that appear in the entire affected population if a specific threshold dose is exceeded. As the dose increases, the symptoms become more pronounced.
- **Stochastic effects:** these are probabilistic effects, thus the frequency of appearance is a function of the X-rays dose. They are an “all-or-nothing” phenomenon, without gradual or progressive manifestations.

The risks related to X-rays exposure for the embryo and the foetus depend on the stage of gestation and on the absorbed dose. They are greater during the period of organogenesis, therefore in the first trimester, while they become lower in the third trimester (Table 16.9) [62].

Nowadays, unfortunately, the legislation does not consider the case of a woman unaware to be pregnant who already underwent to a diagnostic test. In that case, the medical physics expert shall liaise with the radiation protection expert in order to determine the dose administered “a posteriori”.

Table 16.9 Ionizing radiation, foetal and embryonic risks

Risk to embryo and foetus depending on gestational age at time of exposure and dose

Non-implantation (within 3 weeks)
 Spontaneous abortion (within 3 weeks)
 Foetal death (within 3 weeks)
 Body and organ malformations (second and third months)
 IQ impairment (after the third month)
 Severe mental retardation
 Childhood cancer and leukaemia

Doses of 0.1 Sv (100 mGy) in the first month of pregnancy may result in abortion
 Exposure to high doses between 8 and 15 weeks may result in a reduction of 30 points of IQ Sv-1

Modified by Wagner and Appendices [62]

When the embryo cells are undifferentiated and very little (within the first 3 weeks of conception), the most likely damage is inability to implant into the uterine wall or death of the embryo, an event that usually goes unnoticed (ICRP57-60). Exposure of an embryo during the first 3 weeks after fertilization does not appear to give rise to probabilistic or deterministic effects. During the remaining period of the main organogenesis, the radiation may produce malformations in the organs that develop at the time of exposure. In humans, these effects are deterministic in nature.

Therapeutic abortion procedures can be considered when the dose to the foetus or embryo during the first 4 months of pregnancy exceeds 100 mGy, while for doses between 10 and 100 mGy, therapeutic abortion is suggested only when there are further indications (see ICRP 1984) [58–61].

X-ray exams must be performed with the minimum number of projections. In case of tomographic examinations by conventional technique, the radioscopy time and scans must be reduced to a minimum, with accurate beam collimation and shielding, if possible, of the product of conception.

In the case of nuclear medicine, it is necessary to pay particular attention to the choice of radiotracer. It is crucial to minimize the amount of the radiotracer accelerating its elimination.

If there is uncertainty about the state of pregnancy, the investigation or treatment should be performed in accordance with the prior recommendations. When possible, the medical physicist can estimate an “in vivo” dosimetry by recording the technical parameters for the calculation of the X-ray dose administered and absorbed during the exam for further evaluations.

Fluoroscopy

Studies evaluating estimated foetal exposure for cardiac ablation procedures are reassuring for both the radiologist and the patient; in fact, radiation exposure is generally very low, although exposure longer than >35 min may result in a dose of 105 mGy to the uterus.

The dose recorded during spinal procedures is similarly low, when the uterus is out from the radiation beam.

Even if the data in neuroendovascular literature are scarce, it is reasonable to deduce that if the foetus is not included in the X-ray beam, there are no contraindications, once all the precautionary procedures already discussed have been put in place.

Nuclear Medicine

Most procedures use short-lived radionuclides (such as technetium-99 m), which do not involve high foetal doses. In addition, the foetal dose can be reduced by maternal hydration to promote rapid elimination of the radio agent through the urine.

However, some radionuclides cross the placenta and can cause risks to the foetus (iodine-131), particularly after the tenth week when the thyroid of the foetus begins to accumulate iodine. High doses to the thyroid gland of the foetus may result in permanent hypothyroidism.

Nuclear Magnetic Resonance Imaging [63–67]

In the absence of data demonstrating direct embryo toxicity on foetal development, MRI is recommended for pregnant women, if diagnostic alternatives utilise ionizing radiation. However, each case should be considered individually, and MRI can only be performed after the neuroradiologist approval.

Potential damage in the case of MRI includes:

- **Thermal damage:** increased vulnerability during organogenesis, with high susceptibility of the nervous system (first trimester). However, the calculated temperature increase to the foetus is not teratogenic.
- **Noise damage:** high susceptibility of the foetal auditory system to acoustic stimuli, especially after the 24th week, when the auditory system is developed.

Even if it is advisable to avoid MRI within the first 3 months, if necessary it is recommended to use a protocol with short high SAR (specific absorption rate) sequences, possibly interspersed with low SAR sequences.

At the same time, it is necessary to avoid heating the mother, utilizing an adequate ventilation, a low room temperature and avoiding blankets.

It is essential to inform the patient that, to date, no harmful effects have been reported from the clinical use of 1.5 T or less MRI with a field. Since there is no experience with the use of larger magnetic fields, these should be avoided for the time being.

If the abdomen is not the target of the examination, it is recommended to keep the foetus away from the radiofrequency coil.

As maternal warming can reduce placental perfusion, special attention should be paid to patients with placental insufficiency and to patients with impaired thermoregulation or fever.

Contrast Medium [63–67]

There are no specific guidelines for pregnant women or women who have recently given birth. The data reported in the table attached to this paragraph are extrapolated from the ESUR and EFSUMB guidelines (European Society of Urogenital Radiology) (European Federation of Societies for Ultrasound in Medicine and Biology) on contrast media. In general, if possible, it is always better to avoid intravenous contrast medium (CM) during pregnancy. The US Food and Drug Administration classifies iodine-based as class B and gadolinium as class C contrast media.

In class B, animal studies have not shown any risk to the foetus, but there are no methodologically valid and controlled studies in pregnant women or animal studies, at the first and subsequent quarters of pregnancy.

In class C, animal studies have shown toxicity to the foetus, and there are no methodologically valid and controlled studies in

humans, but the potential benefits of the drug could justify its use in pregnant women despite the potential risks to the foetus.

Although the doses used in clinical practice are unlikely to cause adverse effects, currently the use of gadolinium in pregnant women is not recommended. Gadolinium should only be used if the neuro-radiologist believes that the information it can provide will benefit the mother above all potential risks.

The use of gadolinium during breastfeeding is considered safe because the amount excreted in breast milk is very low as well as the amount absorbed by the intestine of the newborn. As a precaution, however, it is recommended to abstain from breastfeeding within 24 h after the administration of gadolinium.

With regard to iodate contrast medium, only a small amount passes into breast milk, while it is not absorbed through the intestine. Therefore no special precaution or cessation of breastfeeding is necessary. Obviously, it is mandatory to obtain the informed consent of the patient before the administration of any contrast medium. Table 16.10 on the use of contrast media and Table 16.11 on diagnostic tests and radiation protection in pregnancy and puerperium are as follows.

Table 16.10 Use of contrast agents in pregnancy and postnatal care [63–67]

	CM iodates	Gadolinium-based CM	Ultrasound CM
Pregnancy	Administer only if strictly necessary. If administered check the thyroid function of the newborn child during the first week of life	When the indication is strictly necessary, administer the lowest possible dose. More stable gadolinium-based contrast media (macrocyclic agents) are preferable. No controls required or precautions for foetus or newborn	Not recommended

Table 16.10 Continued

	CM iodates	Gadolinium-based CM	Ultrasound CM
Breastfeeding	After administration, it is not necessary to suspend breastfeeding	After administration, suspend breastfeeding for 24 h	Not recommended
Pregnant puerpera with renal failure	Beware of adverse renal reactions No precautions necessary for foetus or newborn	Do not administer	Not recommended

Table 16.11 *Key messages* on neuroradiology investigations in pregnancy and puerperium

Neuroradiology imaging should be performed considering that the most important factor for the health of the foetus is the health of the mother

Ionizing radiation must be administered according to the ALARA principle

Ionizing radiation within 50 mGy is not associated with increased incidence of foetus abnormalities or miscarriages

Plain CT in emergency allows to exclude bleeding, hydrocephalus and lesions occupying space

MRI can be performed if clinically indicated using low SAR sequences

Arterial or venous angio-MRI without contrast medium (TOF sequences) are preferable to angio-CT acquisitions

MRI and CT with contrast medium should be avoided but, in selected circumstances, can be performed only if requested by the neuroradiologist

For the study of the spine and the spinal cord, MRI is certainly preferable, although CT scans can be performed after the first trimester if the foetus is not included in the primary X-ray beam, after dose evaluation from the health physicist

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17.

Functional Disorders in Emergency

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Functional symptoms are currently defined as “physical” disorders that are not attributable to an underlying organic disease and of which a psychogenic origin is assumed. The neurological functional

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symptoms (paresis, visual disturbance, tremor, etc.) represent an important challenge for the clinician, due to the high prevalence, the difficulties in the differential diagnosis with various common neurological diseases, and the poor treatment outcomes.

The first problem to deal with in this field is terminology. In the neurological literature, the most common terms are “psychogenic”, an explicit reference to the supposed psychic origin, and “functional”, a more neutral term and therefore preferred among patient associations. However, in the psychiatric literature, reference is mainly made to “Conversion Disorder”, for which the DSM-5 defines precise diagnostic criteria that are reported in Table 17.1, and to “Somatic Symptom Disorders”, characterized by somatic symptoms that bring significant discomfort or cause significant impairment of function and excessive and disproportionate thoughts/concerns (to receive this diagnosis, the subject must persistently show these symptoms, typically for at least 6 months).

In this text, the term “functional” is preferred in consideration of the fact that the current theories on the aetiology of these symptoms include mixed, psychological, biological, and social causes, so a purely psychological model is not appropriate [1].

Table 17.1 DSM V criteria for conversion disorder

A. One or more symptoms of altered voluntary or sensory functions
B. Clinical findings that demonstrate incompatibility between the symptom and recognized neurological or general medical conditions
C. The symptom or deficit is not better explained by another mental or medical disorder
D. The symptom or deficit causes significant distress, psychosocial impairment, or warrants medical evaluation
Specify:
<ul style="list-style-type: none"> • With weakness or paralysis • With abnormal movement (tremor, gait disorders) • With symptoms related to swallowing • With symptoms regarding speech • With epileptic pseudo-seizures or convulsions • With anaesthesia or loss of sensitivity • With specific sensory symptoms • With mixed symptoms

Epidemiology

Neurological functional symptoms (NFS) are common and are the second cause for outpatients' neurological consultations after headache (before Parkinson's Disease and Multiple Sclerosis). A systematic review of 21 European studies found a prevalence of 6% in the general population [2]. Moreover, a multicentre prospective cohort study of 3781 outpatients, examined in hospital neurological settings, found out that in about 16% of cases no symptoms explainable by an organic neurological disease were detected, either totally or partially [3].

History and Clinical Overview

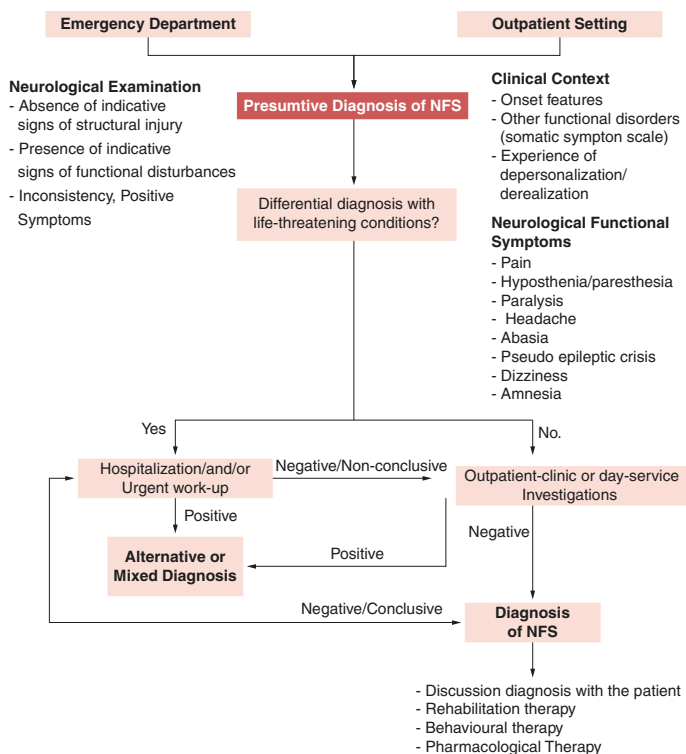
The diagnosis of NFS is complicated and is based on a correct anamnestic framework, on the absence of indicative signs of organic neurological pathology, and, if present, on the detection of indicative signs of functional origin. Adequate diagnostic investigations to exclude possible neurological disorders are necessary in many cases. The algorithm (Fig. 17.1) indicates the main moments of the diagnostic pathway for NFS. When obtained according to these criteria, the diagnosis of NFS has good reliability, and the misdiagnosis rate is of about 5% in most studies [4, 5], comparable to that of major neurological diseases.

The diagnosis cannot be solely based on the clinical history, however there might be various aspects increasing the probability that the symptom is of functional origin and that they therefore need to be taken into account. The patient frequently shows a long clinical history of undiagnosed disorders, which also often affect other branches of medicine and which is useful to research and enhance a correct interpretation.

The most frequently functional symptoms divided by different medical specialties:

- Cardiology: non-cardiac chest pain, benign palpitations
- Otolaryngology: pharyngeal globe, functional dysphonia
- Gastroenterology: irritable bowel, functional dyspepsia

Figure 17.1 Algorithm for patient with suspected functional disturbance



- Rheumatology: fibromyalgia
- Immunology: idiopathic environmental intolerance (*multiple chemical sensitivity*)
- Internal medicine: chronic fatigue syndrome
- Gynaecology: chronic pelvic pain
- Paediatrics: non-specific abdominal pain.

Symptoms that are most frequently of functional origin in the neurological field (in order of frequency):

1. Pain
2. Hypoesthesia/paraesthesia
3. Paralysis
4. Headache
5. Abasia
6. Epileptic pseudo-seizures
7. Dizziness
8. Amnesia

Useful elements in history to raise suspicion of NFS:

- Multiple symptoms,,depression or anxiety
- History of previous functional symptoms or surgery without pathology
- Variability of symptoms
- Critical experiences in childhood, existence of disease patterns in the family, recent stressful events
- Symptoms of autopsychic, somatopsychic, or allopsychic (derealization) depersonalization, the latter commonly associated with panic disorder (Table 17.2)

The Somatic Symptom Scale-8 (Table 17.3) gives a quantitative assessment of the patient's "function" load: a score of 0–3

Table 17.2 Depersonalization and derealization

Depersonalization

I felt weird
 I felt like I was floating
 I felt without my body, detached/disconnected/distanced/distant from myself
 I felt so far away from everything
 I felt in my own place/all alone
 I felt like I was there and at the same time I wasn't
 I could see and hear everything, but I couldn't react

Derealization

The surrounding environment seemed unreal/distant to me
 I felt like I was drugged
 I felt like I was seeing the world through a veil or a glass
 I felt cut off or distant from my surroundings
 Objects seemed smaller/unreal/artificial

Table 17.3 Somatic Symptom Scale-8

During the last week how much were you bothered by the following symptoms?	Not at all	Little	Sometimes	Enough	Very
Stomach or intestine problems	0	1	2	3	4
Back pain	0	1	2	3	4
Pain in arms, legs, joints	0	1	2	3	4
Headache	0	1	2	3	4
Chest pain or shortness of breath	0	1	2	3	4
Dizziness	0	1	2	3	4
Tiredness	0	1	2	3	4
Sleep disorders	0	1	2	3	4
SSS-9 score	=	— +	— +	— +	—

indicates minimum load, 4–7 low, 8–11 medium, 12–15 high, and 16–32 very high.

Neurological Examination

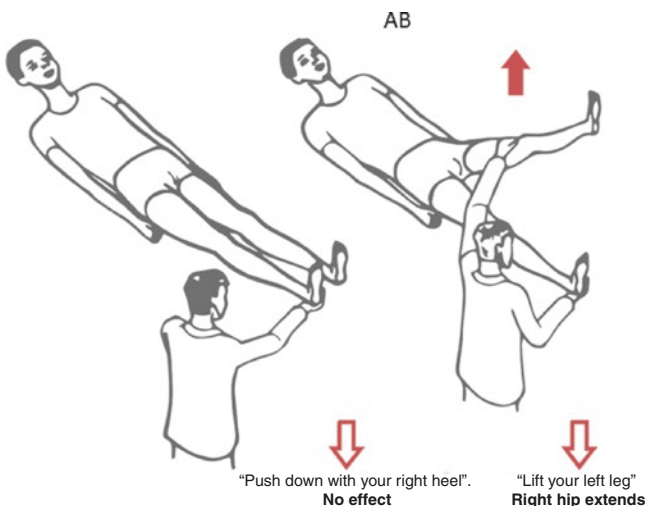
A careful neurological examination by an experienced neurologist is crucial for the diagnosis because it allows on the one hand to exclude objective signs indicative of pathology of the nervous system and on the other to often find inconsistencies or positive signs, indicative of functional disorder.

Non-organic Paralysis

Suspicious inconsistent elements:

- Absence of Babinsky's sign.
- Normal, symmetrical deep tendon reflexes.
- Variable hypostenia.
- Non-selective involvement of flexors and extensors (in central paralysis), involvement that does not respect a root or nerve distribution (in peripheral paralysis).

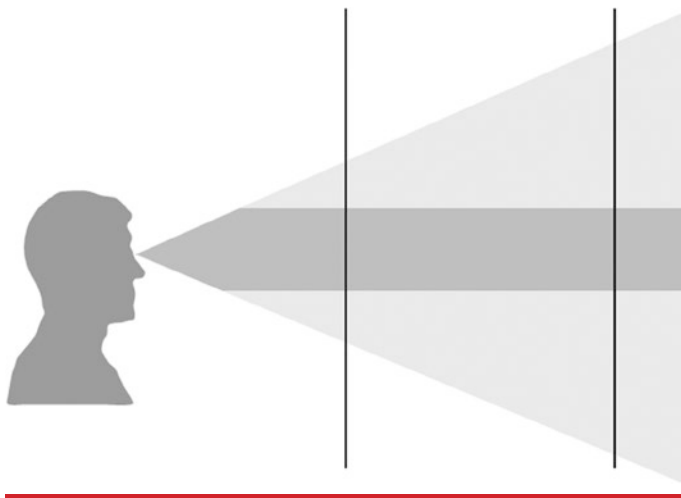
Figure 17.2 **Hoover sign**



- Weakness with sagging limb: limb that falls off with the slightest touch (if the patient has pain, try to get the collaboration by asking him to hold on for a moment).
- Hoover sign: hip-extension hyposthenia does not occur when the patient is asked to flex the contralateral hip against resistance (Fig. 17.2).
- Sign of abduction of the hip: the hyposthenia of abduction of the hip does not occur when the patient is asked to abduct against resistance the opposite hip.
- Dragged gait (the disturbance of the march occurs with dragging of the hyposthenic limb without the characteristics of the "mowing gait" or other pathological neurological gaits).

In **vertigo and disturbances of balance**, the disappearance of symptoms after distracting manoeuvres is indicative of NFS, i.e. the normalisation of the Romberg test asking the subject to identify letters traced on the forehead with closed eyes.

Figure 17.3 **Tubular vision**



In the case of **visual symptoms**, the tests considered indicative of functional disturbances are [6]:

- Fogging test (for monocular visual disturbance): lenses with increasing gradation are applied, which progressively make the image increasingly blurred in the unaffected eye while performing a binocular visual acuity test. The patient who maintains a good visual acuity shows to see well with the affected eye.
- Tubular vision: the patient has a visual field defect of the same width at 1 and at 2 m (Fig. 17.3).

Dystonia and tremors account for between 60% and 90% of all functional movement disorders [7]. Some characteristics of the disturbances appear to support diagnosis:

- Sudden onset
- Static course
- Spontaneous remission
- Paroxysmal symptoms

As with other functional syndromes, some important risk factors for conversion disorders are stressful events, somatizations elsewhere

in the body, psychiatric comorbidity, and a possible benefit from a disease diagnosis.

Features of the neurological examination indicative of a possible functional aetiology of movement disorders:

- Inconsistent and incongruous movement (bizarre break)
- Variability in time (direction, amplitude, frequency, etc.)
- Resolution, or attenuation, with distractibility
- Entrainment

Non-response to therapy is often a useful reinforcing element.

The differential diagnosis between seizures and **epileptic pseudo-seizures**, based on a set of elements sometimes only reported by the subject or by the witnesses, deserves a separate treatment. This is a significant diagnostic problem in epileptology. It is estimated that more than 40% of epileptic subjects also present functional pseudo-seizures [8], complicating the assessment of the response to antiepileptic therapies.

For further information see Chap. 4.

Positive elements suggestive of pseudo-seizures [9, 10]:

- Long duration: seizures lasting more than 2 min and without a clear definition of focal or of generalized seizures
- Cry or scream during the seizures
- Forced eye closure with resistance to opening during the seizures
- Ability to understand and report the events occurring during a seemingly generalized crisis
- Abnormal motor manifestations such as undulatory movements, asynchronous non-rhythmic movements of the limbs, negation movements with the head, opisthotonos

For the role of EEG and video EEG in the differential diagnosis between crisis and pseudocrisis, see the paragraph *Instrumental investigations*.

Instrumental Investigations

The instrumental diagnostic pathway of the subject with NFS is not standardized because it depends on the persistence of reasonable diagnostic doubts after a careful medical history and neurological examination. In some subjects the clinical history and neurological examination may be sufficient; not infrequently the subject comes to the visit with a rich instrumental documentation, already absolutely comprehensive.

Whether the presentation takes place in the context of the emergency department (ED) or in an outpatient context, the first thing to do is to identify, by differential diagnosis, the potentially dangerous conditions for the patient's life: in this case, the diagnostic setting will be developed in the ED. The management of emergencies in the subject with NFS is very problematic and the possibility of discussion with the patient's General Practitioner (GP) or an easy access to the patient's medical records could be a solution in case of emergency. A "fast-track" outpatient pathway should be organized for cases where investigations are necessary but not urgent and also for the continuation of further investigations.

Factors to be taken into account in the presence of suspected NFS:

- The necessary tests to exclude organic diseases should be carried out within a reasonable time frame, so as not to prolong the period of diagnosis uncertainty.
- Extending the exams for several months can cause considerable anxiety and frustration.
- Please note that sometimes it is necessary to make two diagnoses, for example, functional disorder superimposed on multiple sclerosis or seizures and pseudo-seizures. In this respect, it is important to highlight an important change in the criteria of the DSM-5 which concerns the fact that, while medically unexplainable symptoms were a distinguishing feature of many somatoform disorders in the DSM-IV, the diagnosis of somatoform disorder does not require that somatic symptoms be medically unexplainable. In other words, symptoms may or may not be associated with another medical condition. The DSM-5 crite-

ria for the diagnosis of somatic symptom disorder clearly states that it is not appropriate to make a diagnosis of mental disorder just because a medical cause cannot be demonstrated. While DSM-IV was based on the concept of symptoms that had no organic basis, the DSM-5 emphasizes the concept that thoughts, feelings and behaviours about physical symptoms are disproportionate or excessive. It has therefore been noted that patients with heart disease or cancer will experience thoughts/feelings/behaviours at the same time as the disease and that these individuals will satisfy the diagnosis of the disorder with physical symptoms exposing themselves to the risk of being treated without reason. In this case, training, experience, and clinical judgement will then be the guiding principles. This change of perspective definitively removes the mind-body separation still sustained by the DSM-IV and pushes clinicians to carry out a careful and timely clinical evaluation for these patients.

- Explain clearly and in advance what the exams consist of and what result is expected. Helping patients to expect negative results may improve outcome in case of functional symptoms.
- Provide information on the probability of an incidental result not related to the symptoms (about 10-15% in brain MRI).
- Tests are often solicited by the patient, but it should be kept in mind that a meta-analysis [11] indicates that carrying out diagnostic tests does not reassure patients, does not reduce anxiety, nor does it solve the symptoms. However, it determines a small reduction in the number of subsequent clinical visits.
- The patient with NFS may in some cases exaggerate the symptoms or consciously falsify them for the sole purpose of obtaining the doctor's attention or convincing him/her of the severity of the disease (fictitious disorder, also known as Munchausen's S.). This situation must be distinguished from that of patients who completely make up symptoms in order to obtain medical care. The accentuation of symptoms in a medicolegal scenario for economic gain, with clear lying evidence, is called *malinger-ing* and is not a medical diagnosis.

Psychological tests. Tests, such as the Minnesota Multiphasic Personality Inventory, are useful for assessing key personality

characteristics and can be helpful in patients with diagnostic uncertainty after the clinical interview. In addition, psychological testing can help to assess the patient's strengths, decide which treatments are indicated and monitor the impact of treatment over time.

Role of the EEG. In the differential diagnosis between epileptic seizures and functional pseudo-seizures, the EEG can play an important role, although it should be kept in mind that it is not common to be able to record a seizure and that the intercritical tracing is not significant in many epileptic subjects. **Video EEG** may be particularly useful, and it becomes indispensable if the subject questions the diagnosis or if a previously formulated incorrect diagnosis of epilepsy must be changed. It should be kept in mind that some types of seizures, such as frontal lobe epilepsy, may occur with atypical events while the patient is in a state of consciousness, but may not be detected by electroencephalography. For a meaningful diagnosis, it is also necessary to make sure that the recorded event is the same as the one that usually affects the patient.

Electroencephalography can be even more useful if the department performing the examination has a protocol for inducing seizures with suggestion. This procedure can be performed openly, without the need to cheat the patient [12].

Therapy

The treatment of functional neurological disorders is poorly standardized, mainly because of the incomplete understanding of both the pathophysiology and the factors that maintain these conditions. At the same time, it is a clinical condition with an often negative prognosis, with persistence of symptoms in 40–60% of cases, sometimes in the long term up to 10 years. Since these are complex disorders, the guidelines invite us to take into account the different specificities involved either in the evaluation phase or for the treatment, offering a management that considers the subject from a holistic point of view. Several studies that compared psychometric profiles in patients with functional disorders and

control groups did not generally show higher levels of psychiatric comorbidity. Nevertheless, based on the widespread belief of the psychological aetiology of functional disorders, neurologists often direct patients towards a psychiatric evaluation and recommend psychotherapy with the aim of identifying a underlying psychological conflict, and of bringing it to a level of awareness, in order to solve it. Antidepressant drugs can be useful to manage the depressive symptoms and anxiety that typically accompany functional disorders, improving the patient's overall quality of life and promoting a better acceptance of the psychotherapy. Although there is no solid evidence, the results reported by psychotherapy or antidepressant therapy have generally been modest [13, 14]. Regardless of the presence of depressive symptoms, the clinical efficacy of tricyclic antidepressant drugs and serotonin reuptake inhibitors has been demonstrated at usually lower dosing than those used in anxiety disorders and major depression. An integrated approach is generally recommended, both psychopharmacological and psychotherapeutic, which currently represents the *gold standard* in terms of treatment.

Specific psychopharmacological therapies may be helpful in subjects where both interview and psychological tests have identified clear depressive or anxiety traits. In some subjects, discrete improvements of the functional disorder with serotonergic drugs have been described.

In specific situations, rehabilitative and therapeutic behavioural approaches may be useful. Particularly interesting in this regard are the good results reported at the Mayo Clinic, where they apply a protocol of physical and occupational therapy, lasting 5 days, with an improvement in motor disorders in 73.5% of patients [13, 14].

The American Psychiatric Association also points out that "psychotherapy can help the individual change of thoughts and behaviour, thanks to the learning of new strategies to manage pain, stress and the improvement of their functioning".

Within the NICE (National Institute for Health and Care Excellence) guidelines, there are studies that have positively evaluated and

continue to evaluate cognitive-behavioural therapy (CBT) on somatic symptom disorder and related diseases. In particular, there are studies that are considering the effectiveness of mindfulness (CBT-third wave) on the treatment of disorders from somatic symptoms and related diseases. The intervention aims to use techniques of proven effectiveness that, depending on the case, work specifically in the cognitive-behavioural areas concerned, promoting the replacement of dysfunctional thoughts with more functional ones, a decrease in attention focused in a rigid and monothematic way, better adaptive management of stressful events, the processing of traumatic memories, a more conscious access to their needs, more assertive communication, improvement of coping strategies and a more functional interaction with the other.

An essential first step is clarifying with the patient what the diagnosis is and what the meaning of one's symptom is. A clear explanation of the origin of the patient disorders can be useful to facilitate a process of acceptance of the diagnosis. After a thorough evaluation, it will then be possible to establish personalized therapeutic pathways.

The collaboration of the psychiatrist can be essential, but it is important that a multidisciplinary team is created and that all the subjects involved are experts in the field of NFS; otherwise the transfer of patients to other specialists can create frustration and lead to the repetition of unhelpful investigations.

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18.

Neurotoxicological Emergencies

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Introduction

The poisons/toxic agents have been known since ancient times: in the modern era, they have simply multiplied in number, and their easy availability has increased. There is not another field of human diseases with so many causative agents and therefore able to determine a huge variety of effects and different clinical pictures.

In acute toxicology, however, a substance becomes poison only when, through a suitable contact route, it overcomes the body's natural barriers and reaches the target organs or tissues in such high concentrations as to cause harmful effects and intoxication.

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Moreover, acute poisoning is a vast set of diseases of varying severity caused by exposure via different ways to many causative agents (chemicals, drugs, substances of abuse, etc.). The clinical pictures that follow can differ (depending on the number of substances and the relative dose taken) and are often difficult to diagnose and treat. Poisonings/intoxications affect the entire emergency field (emergency services, emergency departments, intensive care units), but it is not uncommon that acutely intoxicated patients are admitted and treated in other specialized units (e.g. neurology units), such as in case of botulism, peripheral neuropathies, etc.

Furthermore, two other factors negatively affect this clinical field: (a) the paucity of precise knowledge on the toxicity of many substances/drugs, and (b) the lack of toxicological training in our university systems. In some cases, this may lead to excessive concern or, conversely, to serious underestimation of the risks related to xenobiotic exposures.

Although controversies still exist in some aspects of the management of the intoxicated patient (e.g. availability and need for urgent analytical toxicology investigations, use of some antidotes), the principles, processes and procedures that characterize the therapeutic approach in the acute phase are today sufficiently accepted in the scientific community. Therefore, they should be the basic knowledge of all the physicians who operate (also as consultants) in the emergency departments (EDs) which most frequently face up to toxicological emergencies. The advice provided by the specialists of the poison centres (PC) is in any case essential to minimize errors and to set the most suitable diagnostic-therapeutic paths, even when specific guidelines and specific diagnostic-therapeutic paths are not yet available [1].

Therefore, the great variability of causative agents and the frequent occurrence of mixed intoxications (more than one agent, such as three to five different drugs) may cause several contemporary neurological signs/symptoms in each patient: considering these important variables, this chapter evaluate:

- Some intoxications of neurological significance, and for which the specialist neurological advice is always required
- Pictures of signs and symptoms that characterize some toxic syndromes (toxidromes) and the relative intoxications, of which

causing agents are included in the following tables to facilitate their identification

- Examples of syndromes that are related to adverse drug effects/reactions (e.g. serotonin syndrome and neuroleptic malignant syndrome)
- Examples of intoxications which, although less frequent, can be of difficult diagnosis (e.g. peripheral thallium neuropathy, ciguatera, tetanus)

For the specific neurological evaluation and for the differential diagnosis of each neurological sign/symptom described in these intoxications, refer to the respective chapter (e.g. stroke, seizures).

As for the other specialties, it is also important that neurologists refer to the specialist in clinical toxicology (in a reference poison centre) for any diagnostic and therapeutic need.

The Neurological Diagnosis in Intoxications/Poisonings

Toxic diseases (poisonings/intoxications) are characterized by a closer and constant relationship between cause and effects than other diseases, and by a latency time between the exposure and the appearance of symptoms that is characteristic for each agent.

The examination of the patient must be accurate and aimed at the search for signs/symptoms that agree with the history (if available) of exposure to the hypothesized agents, or that allow, in absence of anamnestic data, to direct towards specific diagnoses.

Moreover, it must be considered that in clinical toxicology the signs/symptoms present at a given moment can suddenly change for several causes, such as:

- Absorption of further quantities of the same substance (e.g. slow-release formulations of drugs)
- Absorption of other substances (e.g. multiple ingestion)
- In case of slow metabolism of the primary compound in more powerful compounds, sometimes with different effects (e.g. methanol, ethylene glycol)

In addition to the signs and symptoms that characterize some typical syndromes (toxidromes), other elements can guide the diagnosis, such as characteristic smell of the breath, presence of typical lesions, electrocardiographic or radiographic anomalies, biochemical-metabolic abnormalities (e.g. metabolic acidosis, anionic gap), the colour of urine or gastric content/vomiting, or signs of venepuncture/intake of substances of abuse.

Characteristics related to the clinical aspects of intoxications/poisonings:

- Neurological signs and symptoms are present in most cases of intoxication due to drugs (accidental and voluntary), substances of abuse, natural toxins, chemical agents and pesticides.
- The neurological signs and symptoms are the same as those reported in the previous chapters of this book, but they must be related to the chemical cause rather than to an infectious or an organic cause; so, the treatments can be different.
- It is not always easy to distinguish between toxic and non-toxic causes (infectious, organic, etc.) of neurological signs/symptoms: it is therefore important for the neurologist to discriminate between the various causes and to be aware of the most frequent toxicological syndromes. The lists of toxic agents reported in this chapter, even if non-exhaustive, can help in the differential diagnosis.

Given that a large part of the acute intoxications for which patients access EDs is characterized by neurological signs and symptoms, it is impossible to report all the neurotoxic syndromes and all the related causing agents. Therefore, some examples of the following toxicological diseases are reported in this chapter:

- Frequent and/or severe neurotoxic syndromes
- Peripheral neurotoxic syndrome
- Neurotoxic adverse drug reactions

The experience and knowledge of the specialist in clinical toxicology, available 24/7 in the poison centres, will help whenever necessary.

Toxidromes

Toxidromes are defined as toxic syndromes or constellation of sign and symptoms associated with a class of poisons: the clinical characteristics of selected toxidromes are summarized in Table 18.1. The rapid identification of a toxidrome permits to recognize if a specific toxic or class of agents is involved, and may enable a rapid and optimal treatment with the specific antidote (if available).

Therefore, in clinical practice, some **limitations** are represented by:

- Not all the patients present with all the listed signs and symptoms of a toxidrome
- Co-ingestants and mixed exposure may complicate the clinical identification of a toxidrome
- Many poisons do not cause a classical toxidrome (e.g. carbon monoxide)
- Drugs belonging to the same class can cause different clinical effects: for example,
 - The two opioids meperidine and tramadol do not cause miosis
 - The phenothiazines that have anticholinergic effects (and then mydriasis) can cause miosis due to the concurrent α_1 -antagonism
- Vegetable poisons that contain different alkaloids in variable concentrations (e.g. some *Amanita* mushrooms) can cause different syndromes, sometimes prevalently cholinergic and other times anticholinergic

A wide range of acute alteration of mental status may be present in the poisoned patients. In clinical toxicology, a decreased level of consciousness is a relatively common severe complication of poisonings. The list of drugs or toxins that can cause coma is, by definition, not exhaustive because almost any toxin has this capacity. In recent years, moreover, it is increasingly common to observe patients presenting with “excited delirium” (also known as agitated delirium) characterized by the key clinical features of marked agitation and psychotic/violent behaviour with “extraordinary strength”, associated with hyperthermia. Today

Table 18.1 Selected toxidromes that more frequently require a neurological evaluation of the patient

Signs/ symptoms	Toxidromes				Sedative-hypnotic	Sympathomimetic
	Oploid	Anticholinergic	Cholinergic			
BP	Hypotension	Hypertension	Normal		Hypotension	Hypertension
BPM	Bradycardia	Tachycardia	Bradycardia/ tachycardia		Bradycardia	Tachycardia
RR	Bradypnoea/apnoea	Tachypnoea	Bradypnoea/ tachypnoea		Bradypnoea	Tachypnoea
BT	Hypothermia	Hypothermia	Indifferent		Hypothermia	Hyperthermia
Sensorium	Coma	Delirium/agitation	Indifferent		Coma	Agitation
Pupils	Severe miosis	Mydriasis	Indifferent		Miosis	Mydriasis
Peristalsis	Reduced/absent	Absent	Overactive		Reduced	Indifferent/overactive
Sweating	Indifferent	Absent	Increased		Indifferent	Increased
Others	Hyporeflexia	Xerostomia Urinary retention	Salivation Bronchorrhea Diarrhoea Urinary incontinence Fasciculations		Hyporeflexia Hypotonia Ataxia	Tremors Seizures
Potential toxic involved (list not exhaustive)	Heroin, methadone, morphine, oxycodone, fentanyl, clonidine	Atropine, scopolamine, tricyclic antidepressants	Organophosphates, carbamates		Benzodiazepines, barbiturates, ethanol	Cocaine, amphetamines, or amphetamine derivate
Antidote	Naloxone	Physostigmine	Atropine and possibly oximes		Flumazenil	Symptomatic treatment (e. g. benzodiazepines, cold treatment)

Notes: BP blood pressure, BPM beats per minute, RR respiratory rate

stimulant drugs of abuse or new psychoactive substances (NPS) are mainly associated with these clinical manifestations (see specific paragraph).

Toxicological laboratory analysis may support the clinical hypothesis, and the correct interpretation of the results is essential for the definitive diagnosis or the toxidrome identification. However, laboratory tests do not always resolve the diagnostic doubt in the emergency setting. For example, if an old woman presents with severe neurotoxicity in ED after zolpidem overdose, the detection of benzodiazepines in urine (using an immunoassay test) could come back as negative, and the first suspicion will be, probably, a cerebrovascular event (including stroke). In this case, in front of a typical toxidrome, flumazenil administration may completely solve the toxic clinical manifestations. In fact, zolpidem is a type A GABA receptor agonist of the imidazopyridine class (also defined as non-benzodiazepine Z drug) that acts on the same receptor as benzodiazepines, and its effect is completely antagonized by the antidote: but the emergency test on urine can be confusing.

In the following part of this chapter, some schematic information on causing agent and treatment of acute syndromes (opioids, cholinergic, anticholinergics, sedative-hypnotic and sympathomimetic) are reported. The correspondent withdrawal syndromes are not elucidated.

Diagnosis and Treatment of Acute Opioid Syndrome

Several drugs and substances of abuse are opioids (Table 18.2) that act on the specific receptors in the CNS producing the typical toxidrome that require immediate supportive treatment and the administration of the specific antidote naloxone.

The **diagnosis** can be confirmed in EDs through the commonly available “urine drug of abuse panel”. The **limits of the urinary screening for opioids are**:

- False negative analytic results are possible as the test can detect morphine, heroin, monoacetylmorphine, codeine and in some cases hydrocodone and hydromorphone. Instead, semisynthetic

Table 18.2 Selected drugs and substances of abuse causing opioids syndrome (non-exhaustive list)

Drugs	New opioids available in the illegal market (abuse)	
Buprenorphine	<i>New synthetic opioids</i>	<i>Synthetic fentanyl</i>
Butorphanol	Piperidylthiambutene	2-Fluorofentanyl
Codeine ^a	Isotonitazene	Furanylbenzylfentanyl
Fentanyl ^a	2F-Viminol	4-Fluoro-butyrfentanyl (4F-BF)
Dextromethorphan	Bromadoline	Cyclopropylfentanyl
Diphenoxylate	Butorphanol	Methoxyacetyl fentanyl
Hydrocodone	Embutramide	Tetramethylcyclopropanefentanyl
Hydromorphone	ODT	4-Fluoro-cyclopropylbenzylfentanyl
Levorphanol	Tianeptine	4F-furanyl fentanyl
Loperamide	3,4-Methylenedioxy-U-47700	Furanyl fentanyl
Meperidine	Isopropyl-U-47700	2-Methylacetyl fentanyl
Methadone ^a	U-49900	(Iso)butyl-F-fentanyl <i>N</i> -benzyl analogue
Morphine ^a	U-48800	Crotonyl fentanyl
Nalbuphine	<i>N</i> -Methyl U-47931E	Valeryl fentanyl
Nalmefene	AP-237	Cyclopentyl fentanyl
Nalorphine	2-Methyl-AP-237	3-Fluoromethoxyacetyl fentanyl
Oxycodone ^a	AH-7921	Ocfentanil (A-3217)
Oxymorphone	U-50488	Tetrahydrofuranlyfentanyl (THF-F)

Paregoric	U-47700	4-Fluoro-isobutyrfentanyl (4F-iBF)
Pentazocine	MT-45	Thiophenefentanyl
Propoxyphene	U-51754	Butyrfentanyl
Tramadol ^a	Isotonitazene	4-Chloro-isobutyrfentanyl (4Cl-iBF)
Fentanyl		Benzoylfentanyl
Tapentadol		Benzylfentanyl
Heroin ^b		Benzodioxole fentanyl
		3-Fluorofentanyl (meta-fluorofentanyl)
		Acryloylfentanyl
		Acetylbenzylfentanyl
		Acetylfentanyl
		Alpha-methylfentanyl butanamide analogue
		Carfentanil
		3-Phenylpropanoylfentanyl
		3-Methylcrotonylfentanyl
		4-Hydroxybutyrfentanyl/4-HO-BF
		Benzoylbenzylfentanyl
		Despropionyl-2-fluoro fentanyl
		4-Methoxybutyrfentanyl (4-MeO-BF)

^aUsed also as substances of abuse

^bDiacetylmorphine, used therapeutically in some countries

opiates derived from morphine show variable cross-reactivity, and fully synthetic opioids (e.g. fentanyl, meperidine, methadone, propoxyphene, oxycodone, tramadol, tapentadol) have minimal or no cross-reactivity. Therefore, the new synthetic drugs of abuse (new fentanyls and other new opioids) are not detected.

- False positive analytic results responses can be due (a) to a past assumption, not contextual to the clinical picture (urine test can be positive until 2–3 days after heroin assumption), or (b) to a cross-reactivity with rifampin and ofloxacin and other quinolones in some immunoassays.

Methadone, oxycodone and many other opioids that are not usually detected by routine opiate screen may require separate specific immunoassays (separate testing for methadone is sometimes available).

Antidotal Treatment

- Naloxone may be administered intravenously, intranasally or intramuscularly, at boluses of 0.4–2 mg. If the administration is followed by a rapid positive clinical response, the diagnosis *ex adjuvantibus* is also obtained. In case of no response to 4–10 mg, it is necessary to consider another cause or a co-intake of other poisons
- The antidote has a short half-life: continuous infusion is required in patients intoxicated with long half-life opioids (e.g. methadone) or by ingestion of tablets (e.g. oxycodone) or packages (body packers)
- No real contraindication exists to the administration of naloxone in emergency settings: the only possible (mild) adverse reaction is the appearance of withdrawal symptoms in patients with opioid addiction.

Diagnosis and Treatment of Acute Cholinergic Syndrome

Acute cholinergic syndrome, a potentially lethal poisoning, is related to the increased acetylcholine activity on central and peripheral muscarinic and nicotinic receptors. The syndrome can be caused by either acetylcholinesterase enzyme inhibition (e.g. organophosphorus and carbamate compounds) or direct agonist action at muscarinic and nicotinic receptors (Tables 18.3 and 18.4).

Table 18.3 Substances causing cholinergic syndrome due to acetylcholinesterase inhibition

<i>Organophosphorus compounds</i>	<i>Carbamate insecticides</i>	Anticholinesterase agents used in dementia
Azinphos-methyl	Aldicarb	Donepezil
Chlorpyrifos	Carbaryl	Galantamine
Coumaphos	Ethiofencarb	Rivastigmine
Diazinon	Fenoxycarb	Tacrine
Dichlorvos	Fenthion	Agents used in myasthenia gravis
Dimethoate	Methiocarb	Edrophonium
Fenthion	Methomyl	Neostigmine
Malathion	Pirimicarb	Pyridostigmine
Methamidophos	Propoxur	Antidotes
Parathion	Thiodicarb	Physostigmine
Pirimiphos-methyl	<i>Chemical warfare agents</i>	
Trichlorfon	Tabun	
Phosmet	Sarin	
Methyl parathion	Soman	
Terbuphos	VX	

Table 18.4 Substances causing cholinergic syndrome as acetylcholine agonists

<i>Direct muscarinic agonists</i>	<i>Direct nicotinic agonists</i>	<i>Indirect nicotinic agonists</i>
Acetylcholine	Nicotine	Chlorpromazine
Aceclidine	Carbachol	Ethanol
Bethanechol	Coniine	Ketamine
Carbachol	Cytisine	Local anaesthetics
Pilocarpine	Lobeline	Phencyclidine
Arecoline	Succinylcholine	Volatile anaesthetics
Cevimeline	Varenicline	Muscarine-containing mushrooms
Methacholine		<i>Inocybe</i> species
Muscarine		<i>Clitocybe</i> species

The signs and symptoms are reported in Table 18.1: they are a constellation of CNS, autonomic and neuromuscular effects. The most evident effect is the copious secretion, vomiting, diarrhoea and altered mental status, fasciculation and muscle weakness. Death is consequent mostly to excessive respiratory secretions, bronchospasm and muscular paralysis.

This syndrome requires immediate **diagnosis**, which is clinical: no specific toxicological analysis is available in emergency settings, excluding the determination of plasma cholinesterase activity in organophosphates and carbamates poisonings.

The **specific treatment** is made using one or two antidotes, in relation to the causal agent:

- Atropine: intravenous boluses of 0.5–1 mg; in case of organophosphorus intoxication, repeated doses of 2 mg until the disappearance of bronchorrhea
 - Adverse reactions due to high dosages are agitation and delirium
 - There is no contraindication if the diagnosis is correct
- Oximes administration follows the correct atropinization of the patient: its use is generally limited to organophosphorus compounds poisonings.

Diagnosis and Treatment of Acute Anticholinergic Syndrome

The acute anticholinergic syndrome, a potentially lethal intoxication, is due to the competitive inhibition of central and peripheral acetylcholine muscarinic receptors (Table 18.5).

The signs and symptoms (reported in Table 18.1) are a characteristic “agitated delirium” (fluctuating mental status, confusion, restlessness, fidgeting, visual hallucinations, picking of object in the

Table 18.5 Substances causing anticholinergic syndrome

Antiparkinson drugs	Topical ophthalmologic agents	Antipsychotics
Amantadine	Cyclopentolate	Chlorpromazine
Benztropine	Homatropine	Droperidol
Antihistamines	Tropicamide	Haloperidol
Brompheniramine	Direct muscarinic antagonists	Fluphenazine
Chlorpheniramine	Atropine	Trifluoperazine
Cyproheptadine	Anisotropine	Atypical antipsychotic
Dexchlorpheniramine	Hyoscyamine	Olanzapine
Dimenhydrinate	Glycopyrrolate	Quetiapine
Diphenhydramine	Trihexyphenidyl	Clozapine
Doxylamine	Cyclobenzaprine	Plants and herbal remedies
Pheniramine	Orphenadrine	<i>Datura stramonium</i>
Promethazine	Scopolamine-hyoscine	<i>Solanum</i> spp.
Trimeprazine	Other quaternary amines	<i>Atropa belladonna</i>
Antitussives	Clidinium	<i>Mandragora officinarum</i>
Dextromethorphan	Dicyclomine	<i>Hyoscyamus niger</i>
Antidepressants	Ipratropium bromide	Other tertiary amines
Tricyclic antidepressants	Isopropamide	Biperiden
Urinary antispasmodic agents	Mepenzolate	Darifenacin
Oxybutynin	Methantheline	Flavoxate
Anticonvulsant agents	Methscopolamine	Fesoterodine
Carbamazepine	Propantheline	Oxybutynin
	Tiotropium	Oxyphencyclimine
	Tridihexethyl	Procyclidine
	Tropium chloride	Tolterodine

air, mumbling slurred speech, disruptive behaviour) accompanied by a variety of central (tremor, myoclonus, coma, seizures) and peripheral effects (mydriasis, tachycardia, dry mouth, dry skin, flushing, hyperthermia, scarce or absent bowel sounds, urinary retention) due to muscarinic blockade. The duration of the agitated delirium is not predictable: it may persist for up to 5 days in some circumstances (e.g. deliberate self-poisoning with benzotropine or carbamazepine).

This syndrome requires immediate **diagnosis**, which is clinical. No specific toxicological analysis is usually available in emergency settings for these agents: the detection of anticholinergic alkaloids (e.g. atropine, scopolamine) on biological fluids can be carried out in second-level laboratories.

The **treatment** of the severe CNS effects is made using the specific antidote physostigmine and/or benzodiazepines:

- Physostigmine: 0.5–1 mg by slow i.v. administration (over 2–5 min). Physostigmine is a reversible inhibitor of acetylcholinesterase whose tertiary amine structure allows it to penetrate the blood-brain barrier (neostigmine cannot penetrate into the CNS and can be used only to control peripheral symptoms, such as functional ileus)
 - Adverse reaction to physostigmine: bradycardia, seizure (for rapid administration or excessive dosage), cholinergic symptoms (e.g. vomiting, diarrhoea, hypersalivation)
 - Contraindication: in severe tricyclic antidepressant overdose, physostigmine may worsen cardiac conduction disturbances. Do not use concurrently with depolarizing neuromuscular blockers (e.g. succinylcholine)
 - Use for the diagnosis ex adjuvantibus: at low doses, physostigmine can be used (monitoring the cardiac function) to differentiate functional psychosis from anticholinergic delirium
- Benzodiazepines can be used if physostigmine is not available: diazepam 5–10 mg PO or i.v. every 15 min until tranquilization is obtained.

Diagnosis and Treatment of Acute Sedative-Hypnotic Syndrome

The acute sedative-hypnotic syndrome, a potentially lethal intoxication, is due to agent that modulates the activity of the GABA-neurotransmitter complex (gamma aminobutyric acid) (Table 18.6). The enhancement of the inhibitory GABA_A activity results in CNS generalized depression. The relevant signs and symptoms are reported in Table 18.1: drowsiness, ataxia, nystagmus, slow gastric motility, profound hypotonia, coma and respiratory arrest are the typical clinical effects, frequently associated with hypotension and depression of the cardiac contractility (barbiturates). Baclofen, which is a GABA_B receptor agonist, produces profound CNS and respiratory depression associated with paradox muscle hypertonia and seizure-like activity.

Margin of safety in benzodiazepine overdose is much greater compared to barbiturate overdose, where unintentional lethal dosing is not uncommon.

This **diagnosis** is clinical: some specific toxicological analyses are available in emergency settings, usually in urine, to detect benzodiazepines (BDZ) and barbiturates, although not all of the molecules of these families are detectable by the first-level tests

A specific **treatment** (antidote) is available only for BDZ:

- Flumazenil: intravenous boluses of 0.5–2 mg, repeatable as needed; continuous infusion may be useful in severe BDZ intoxications

Table 18.6 (Families of) drugs causing sedative-hypnotic syndrome

Benzodiazepines	Barbiturates	Baclofen
Glutethimide	Paraldehyde	Methaqualone
Bupirone	Ethchlorvynol	Chloral hydrate
Z-drugs (non-benzodiazepine agents)	Meprobamate	GHB (gamma hydroxybutyrate)/gamma butyrolactone (GBL)

- ❑ Flumazenil may be used in the diagnosis *ex adjuvantibus* if clinical presentation is characterized exclusively by signs and symptoms of BDZ poisoning (miosis, hypotonia, CNS depression) in absence of mydriasis, tachycardia or hypertonia
- ❑ Adverse reactions due to high dosages are agitation and delirium
- ❑ Contraindication: epilepsy being treated with BDZ and mixed BDZ intoxication with other drugs with CNS excitatory effects (e.g. antidepressants).

Diagnosis and Treatment of Acute Sympathomimetic Syndrome.

Several agents cause the acute sympathomimetic syndrome, a potentially lethal intoxication (Table 18.7). All the xenobiotics producing pharmacologic effects that result in (or mimic an) increased activity of the adrenergic nervous system are sympathomimetics. Examples are α - and β -adrenoceptor agonists, monoamine oxidase inhibitors (MAOIs) and several drugs of abuse, the most frequent of which are the amphetamines group (see below). The pharmacological specificities of these agents and the different kinetics lead to different clinical features, but have in common sympathomimetic and excitatory effects such as agitation, convulsions, hypertension, tachycardia, hypertonia, hyperthermia, arrhythmias, etc.

The **diagnosis** confirmation in EDs can be obtained through the **urinary screening test** only for some substances of abuse (e.g. cocaine, MDMA, amphetamines). The major limits of this kind of analytical determination are:

- False negative results are usual for the new psychoactive substances and for pharmaceutical drugs
- False positive results are possibly due to a previous assumption not contextual to the current clinical problem.

There is no specific antidote treatment: therapy is based on the treatment of symptoms, mainly with sedative drugs (e.g. benzodiazepines).

Table 18.7 Substances causing sympathomimetic syndrome (non-exhaustive list)

Direct acting α-adrenoceptor agonists	Selective α2-adrenoceptor antagonists	Inhibition of norepinephrine uptake and indirect acting agents
Epinephrine	Idazoxan	Amphetamine
Ergot alkaloids	Efaroxan	Cocaine
Methoxamine	Yohimbine	Fenfluramine
Midodrine	Imidazoline binding site antagonists	Methylphenidate
Norepinephrine	Idazoxan	Pemoline
Phenylephrine	Efaroxan	Phenmetrazine
β-Adrenoceptor agonists	MAOIs—indirect acting agents	Propylhexedrine
Albuterol	Amphetamine metabolites	Tyramine
Dobutamine	Clorgyline	Atomoxetine
Epinephrine	Isocarboxazid	Benztropine
Isoproterenol	Linezolid	Bupropion
Metaproterenol	Moclobemide	Carbamazepine
Norepinephrine	Pargyline	Cyclic antidepressants
Terbutaline	Phenelzine	Diphenhydramine
Mixed acting agonists	Rasagiline	Duloxetine
Dopamine	Selegiline	Orphenadrine
Ephedrine	Tranlycypromine	Reboxetine
Mephentermine		Tramadol
Metaraminol		Trihexyphenidyl
Phenylpropanolamine		Venlafaxine
Pseudoephedrine		

Regardless of the toxidromes reported above, when the patient presents some signs and symptoms, it can be useful to consider, at least as a differential diagnosis, the possibility that the clinical picture may be due to drugs or poisons. Therefore, some major neurotoxic signs and symptoms and their main causative agents are reported below.

Toxic Coma and Stupor

Almost any toxin has the potential to depress the mental function causing stupor and coma. A decreased level of consciousness is one of the most common serious manifestations of drug overdose or poisoning: a non-exhaustive list of causing agents is reported in Table 18.8.

Table 18.8 Toxic agents that commonly cause stupor or coma as primary effect

Anticonvulsants	Alcohols	Chemical agents
Carbamazepine	Ethanol	Carbon monoxide
Lamotrigine	Methanol	Cyanide in fires
Tiagabine	Isopropyl alcohol	Hydrogen sulphide
Valproic acid	Ethylene glycol	Methemoglobinemia
Antipsychotic agents	Sedative-hypnotic agents	Hydrocarbons
Amisulpride	Barbiturates	Toluene
Chlorpromazine	Benzodiazepines	Eucalyptus oil
Olanzapine	GHB (gamma hydroxybutyrate)	Local anaesthetics
Quetiapine	Non-benzodiazepine agents (Z-drugs)	Bupivacaine
Clozapine	Bromides	Lidocaine
Lithium	Centrally acting α_2-agonists	Ropivacaine
Antidepressants	Clonidine	Substances of abuse
Serotonin reuptake inhibitors	Oxymetazoline	Opioids (classic and new)
Tricyclic antidepressant	Cholinergic agents	Anticholinergic
Antihistamines	Carbamates	GHB-GBL
Diphenhydramine	Dementia acetylcholinesterase inhibitors (e.g. donepezil)	Other drugs
Antimalarial agents	Nicotine	Baclofen
Chloroquine	Organophosphates	Propranolol
Hydroxychloroquine		
Quinine		

In a (potentially) poisoned patient, coma may be the result of:

- Direct toxic effect on the CNS
- Secondary effect of poisoning on CNS (e.g. hypoxemia, hypoglycaemia, cerebral oedema, seizures, etc.).

With a few important exceptions, the majority of toxic agents that cause toxic coma produce a relatively benign and temporary alteration that has a good prognosis with thorough appropriate (supportive and/or antidote) treatments. In selected cases (e.g. opioid, benzodiazepines), the prompt antidote administration (at an enough dose) together with a supportive care can promptly reverse the clinical picture.

Toxic Seizures

Seizures are one of the major neurotoxic effects due to medication and drug of abuse overdose (Table 18.9). Toxic seizures are usually generalized, sometimes self-limiting and easily controlled with intravenous benzodiazepines; phenytoin is not indicated in the management of toxic seizures. In selected cases, a specific antidote can be the first-line treatment (e.g. isoniazid and other hydrazines intoxication) (see antidote list, Table 18.25).

Toxic Agitation, Delirium and Psychosis

Delirium is an altered conscious state with impaired cognition. Agitation, delirium and psychosis can be caused by a variety of drugs and toxins (Table 18.10), as well as to a functional disorders or to metabolic encephalopathy due to medical illness. In the majority of the cases:

- Sensorium is intact and hallucinations are predominantly auditory in functional psychosis and in stimulant-induced agitation and psychosis
- Sensorium is usually altered (manifested by confusion or disorientation) and hallucinations are predominantly visual in metabolic encephalopathy or drug-induced delirium.

Table 18.9 Examples of drugs/class of drugs, substances of abuse, toxins and withdrawal syndromes causing seizures

Anticonvulsants	Antidepressants	Other medications
Carbamazepine	Bupropion	Quinidine
Topiramate	Citalopram	Theophylline
Lamotrigine	Tricyclic antidepressant	Lidocaine and other local anaesthetics
Antimalarial agents	Serotonin reuptake inhibitors	Propranolol
Chloroquine	Venlafaxine	Isoniazid
Hydroxychloroquine	Antipsychotic agents	Amoxapine
Quinine	Butyrophenones (haloperidol and droperidol)	Salicylates
Hypoglycaemic agents	Phenothiazines	Mefenamic acid
Insulin	Olanzapine	Atropine
Sulfonylureas	Quetiapine	Substances of abuse
Opioids	Loxapine	Caffeine
Tramadol	Clozapine	Ecstasy (MDMA)
Dextropropoxyphene	Lithium	Amphetamines and derivatives
Pethidine	Pesticides/insecticides/repellent	Cocaine
Antihistamines	Cholinergic agents (carbamates, nicotine, organophosphates)	Ephedrine
Diphenhydramine	Camphor	Phenylpropanolamine
Toxic cellular hypoxia	Chlorinated hydrocarbons	Phencyclidine (PCP)
Carbon monoxide	Fipronil	Synthetic cathinones ("bath salts")
Cyanide	Methaldehyde	Synthetic cannabinoids
Hydrogen sulphide	Other toxic agents	GHB (gamma hydroxybutyrate)
Other agents	Cicutoxin (water hemlock)	Withdrawal from ethanol or sedative-hypnotic drugs
Methanol	Other plant toxins	Ethanol
	Anticholinergic plants	Barbiturates

Table 18.10 Selected drugs and toxins causing confusion, delirium, agitation and psychosis

Confusion or delirium (predominant)	Agitation or psychosis (predominant)
Amantadine	Amphetamines and derivatives
Anticholinergic agents	Caffeine and theophylline
Antihistamines	Cocaine
Lithium	Synthetic cathinones
Carbon monoxide	Dextromethorphan
Levodopa	LSD (lysergic acid diethylamide)
Disulfiram	Marijuana
Salicylates	Phencyclidine (PCP)
Nicotine	Ketamine
Lidocaine and other local anaesthetics	Dimethyltryptamine
Benzodiazepines	Synthetic cannabinoids
Marijuana	Serotonin reuptake inhibitors (SSRIs)
Serotonin syndrome	Steroids (e.g. prednisone)
Neuroleptic malignant syndrome	Cycloserine
Withdrawal from ethanol or sedative-hypnotic drugs	Procaine
	Ethanol
	Antidepressants (bupropion, venlafaxine)

Anticholinergic delirium is often accompanied by tachycardia, dilated pupils, flushing, dry skin and mucous membranes, decreased peristalsis and urinary retention (central anticholinergic syndrome). As in other intoxications, the treatment of the central anticholinergic syndrome is based on the rapid administration of a specific antidote (physostigmine) (see the section “Diagnosis and Treatment of Acute Anticholinergic Syndrome”).

The alteration of the CNS functions is usually a transient direct toxic effect that resolves along with other features of intoxications, even if prolonged and possibly chronic psychosis can be a sequel of the new psychoactive substance toxicity.

Toxic Dystonia, Dyskinesia and Rigidity

Abnormal movement and rigidity are relatively common in clinical toxicology, primarily as adverse drug reaction of therapeutic treatments but also because of toxic doses intake [2] (Table 18.11):

- Dystonic reactions are frequently related to central dopamine blockade, mostly by antipsychotic agents and antiemetics.
- Dyskinesias are related to an increase in central dopamine activity or to a blockade of central cholinergic effects.
- Rigidity is typical of NMS (neuroleptic malignant syndrome) and serotonin toxicity.

Table 18.11 Selected drugs and toxins causing dystonia, dyskinesia and rigidity

Acute dystonic reactions	Dystonia and/or akathisia
Amphetamines	Haloperidol and droperidol
Anticholinergic agents	Metoclopramide
Antihistamines	Phenothiazines (prochlorperazine)
Bismuth	Ziprasidone and other atypical antipsychotic agents
Caffeine	Rigidity
Carbamazepine	Black widow/malmignatta spider bite
Carisoprodol	Lithium
Cocaine	Malignant hyperthermia
GHB (gamma hydroxybutyrate)	Manganese
Ketamine	Methaqualone
Levodopa	Monoamine oxidase inhibitors
Lithium	Neuroleptic malignant syndrome
Phencyclidine (PCP)	Phencyclidine (PCP)
Serotonin reuptake inhibitors (SSRIs)	Strychnine
Venlafaxine (SNRI)	Tetanus
Methylphenidate	
Rivastigmine	
Linezolid	
Tricyclic antidepressants	

Treatment

- Benzodiazepines are the first choice for both toxic dystonia reactions and dyskinesia.
- Treatments such as dantrolene, bromocriptine and specific anti-venoms can be employed in rigidity due to specific agents and venoms.

Frequent and/or Severe Neurotoxic Syndromes

Among the neurotoxic syndromes that most frequently require an accurate neurological evaluation in the emergency setting, there are the carbon monoxide poisoning (more frequent, sometimes due to fire smoke exposures) and the botulinum poisoning, rarer but possible cause of delays and diagnostic errors.

Carbon Monoxide Poisoning

Three important **milestones** regarding the medical evaluation of carbon monoxide-poisoned patients:

1. Why consider carbon monoxide (CO) poisoning in the differential diagnosis of many neurological signs/symptoms? because CO is the cause of
 - (a) Various neurological symptoms at presentation to EDs
 - (b) Many unnecessary procedures and tests (e.g. encephalic CT scan) if it is not quickly identified
 - (c) Important and definitive neurological sequelae if not identified and appropriately and quickly treated
2. When is CO poisoning mainly of neurological competence? in the evaluation of acute damage, but especially in the evaluation of the neurotoxic sequelae (comprehending the neuropsychiatric evaluation in children) that are the most frequent
3. What kind of major risk can be related to the erroneous non-identification of CO poisoning in patients who have compat-

ible symptoms (e.g. headache, dizziness, syncope) but who are discharged and postponed to future medical investigations? a life-threatening re-exposure in a risky environment (e.g. home)

Carbon monoxide (CO) is an odourless and colourless gas (and for these properties commonly nicknamed “silent killer”) generated as consequence of partial oxidation of carbon-containing compounds and finally for incomplete combustion [3].

The more frequent causes of unintentional non-fire-related CO intoxication typically include malfunctioning fuel-burning apparatus such as furnaces, motor vehicles, stove/gas ranges, gas line leakage, water gas and kerosene room heaters, portable generators, fireplaces or in-home burned charcoal [4].

Although occasionally might be self-harmed, the CO intoxication is in most cases unintentional. **Epidemiology of CO poisoning:**

- It is currently the most common type of fatal inhalational poisoning in most countries [5]
- It is unquestionably the leading cause of unintentional poisoning deaths in the Western countries [6]. The US Centers for Disease Control and Prevention (CDC) [7] reports that CO poisoning has an incidence of 23.2 per 1 million population per year, and is responsible for nearly 15,000 emergency department visits and 500 deaths each year.

The current statistics about mortality and morbidity from CO poisoning are strongly biased by substantial under-reporting or misdiagnosis. The transient duration of symptoms in mild intoxication, the ubiquitous and occult nature of exposure and the symptoms that can be confused with other diseases play a critical role in erroneous or late diagnosis. For these reasons, CO is also named “the great imitator”. **Missed diagnosis** of CO poisoning is related to the great variability of the clinical presentation, common to many other diseases:

- The most frequent signs and symptoms may include nausea, vomiting, headache and dizziness, which can suggest other diagnosis such as flu-like syndrome or food poisoning

- The presence of behavioural abnormalities may lead the CO-poisoned patient to psychiatric ward or to erroneous sedatives administration
- Common manifestations in paediatric patients include gastrointestinal disorders and mimic a flu-like syndrome or acute gastroenteritis leading to a frequent potential misdiagnosis [8].

A first study conducted about 40 years ago was undertaken to establish the true incidence of CO-poisoning missed diagnosis. The wrong diagnoses involved 30% (48/162) acutely CO-poisoned patients admitted to the ED during a 3-year period study (1975–1977). Misdiagnosis involved mainly cases presenting neurological (e.g. ischemic cerebral disease, cerebral haemorrhage, cerebral neoplasia, migraine), psychiatric (e.g. hysteria, delirium, mental confusion) and cardiorespiratory (e.g. angina and pulmonary oedema) emergencies. In some cases, also alcohol and food poisonings have been erroneously suspected [9, 10].

Clinical Manifestations and Neurotoxicity

The central nervous system and the heart are the most important target organs in CO poisoning. The most frequent **signs and symptoms** include:

- Nausea, vomiting, diarrhoea (children)
- Headache, dizziness, loss of judgment, mental confusion, disorientation, nausea, vomiting, fatigue, visual disturbance, syncope up to loss of consciousness and coma
- Rhabdomyolysis, pulmonary oedema, retinal haemorrhages and papilledema secondary to cerebral oedema are potential complications
- Cardiac dysfunction and CO-induced myocardial necrosis associated with tachypnoea, tachycardia and hypotension [11–13], even in paediatric patients [14]
- Severe psychiatric impairment, amnesia, behavioral changes, and/or neurological sequelae characterized by parkinsonism, chorea, choreoathetosis or peripheral neuropathy may be further delayed by 2–28 days after acute poisoning.

Several toxic mechanisms (transport and tissue hypoxia, reoxygenation injury and production of oxygen radicals, lipid preoxygenation, inflammation, etc.) finally cause tissue and cellular (mitochondrial) hypoxia. At brain level, some regions are particularly sensitive to hypoxic damage (e.g. cerebral cortex, white matter, basal nuclei and Purkinje cells of the cerebellum). In case of associated hypotension, cerebral regions with relatively poor vascularization and high oxygen metabolism such as *globus pallidus* may be more vulnerable. Brain CT, MRI, MRS and neuropsychological testing are useful tools in diagnosis of CO toxicity and its severity. Moreover, PET and SPECT may provide additional information [15].

The **diagnosis of CO poisoning is essentially clinical and requires high level of suspicion**: major helping aspects are:

- Sudden onset of symptoms
- Preferential occurrence of signs and symptoms in the same space and time
- Clustering within group of peoples
- Co-existence with the use of heaters
- The rapid execution of the crucial diagnostic test (the carboxy-haemoglobin—COHb—blood concentration) whenever there is a suspicion may be crucial in the early and correct diagnosis of CO poisoning.

The COHb value confirms the effective exposure to CO. However, COHb value does not correlate exactly with the clinical severity of CO poisoning, and must not be used as prognostic factor.

Treatment

- Oxygen is the antidote in this poisoning, and patients should be treated immediately:
 - High-level normobaric oxygen (NBO) administration is the milestone of the treatment and should be immediately administered to all poisoned patients
 - Hyperbaric oxygen (HBO) should be reserved to severe poisonings, children and pregnant women. Loss of consciousness, neurological deficits or cardiovascular toxicity generally indicates severe poisoning

- The main indication for the HBO treatment in the moderate and severe cases is the prevention of delayed neurotoxic sequelae, a recurrent transient neuropsychiatric consequence that produces a spectrum of varying symptoms [16].

The treatment of CO-poisoned patients must not be based solely on the COHb levels.

Fire Smoke Inhalation and Mixed Carbon Monoxide-Cyanide Poisoning

Mixed carbon monoxide-cyanide (CO-CN) poisoning may occur after fire smoke inhalation. In most cases COHb may be negative despite toxic or lethal concentrations of CN. In fact, fire smoke is a heterogeneous compound whose chemical composition depends on the combusted materials and the availability of oxygen. The release of hydrogen cyanide may result from the combustion both of natural (e.g. wool, cotton, silk) and of synthetic materials (e.g. polyurethane, polyacrylonitrile, polyamide). The more nitrogen compounds a substance contains, the greater is the potential release of hydrogen cyanide during combustion [17–19]. The co-presence of CO from burning materials may play a critical/synergic role in toxic effects due to fire smoke inhalation. Cyanide has a profound hypoxic effect with cardiovascular manifestations and neurotoxicity [20].

Smoke inhalation is present in about 22% of all burn presentations and in 60% of facial burns [21]. Mortality data for smoke inhalation is disconcerting: at least 30% of burn patients with smoke inhalation injury die, compared with 2% of those without this type of injury [22]. Overall, burns are a leading cause of accidental death, and smoke inhalation is the major contributor to the morbidity and mortality associated with serious burns [23].

In fire smoke inhalation, headache, dizziness, unconsciousness, palpitations, hypotension, confusion, hyperventilation, arrhythmia, apnoea and soot in the mouth and nose have been reported as clinical signs of CO/CN poisoning. Severe lactic acidosis, seizures, hypotension, bradycardia, coma and eventually respiratory and cardiac arrest are present in severe intoxications [24].

Some studies [20] indicate the following **criteria to suspect CN poisoning in fire smoke inhalation** patients:

- Neurologic dysfunction (mental status changes, loss of consciousness) and seizures
- Hypotension
- Bradypnoea
- Presence of carbonaceous materials in the pharynx of sputum
- Metabolic acidosis (serum lactate greater than 8 mmol/L)

Particularly, clinical findings such as coma, pronounced drop in blood pressure, decreased respiratory frequency and increased PaCO₂ levels are associated with increased risk of fatal outcome from fire smoke inhalation [20, 24].

Some clinical differences may help in the differential diagnosis between pure CO intoxication and mixed CO-CN intoxication when there has been exposure to fire smoke (Table 18.12).

Treatment. In addition to oxygen, three families of antidotes are available (see also Table 18.25): cobalt compounds (dicobalt edetate, hydroxocobalamin), sulphur donors (thiosulphate) and the less used methaemoglobin-forming agents [nitrites, 4-dimethylaminophenol (4-DMAP)]. In particular, cobalt compounds and sulphur donors are very effective antidotes in cyanide poisoning:

- Hydroxocobalamin detoxifies cyanide by binding it to form cyanocobalamin (vitamin B12), a non-toxic compound excreted in urine. The regimen should be 5 g i.v. in adults (70 mg/kg in children), repeated in severe cases. Hydroxocobalamin appears

Table 18.12 Key signs and symptoms in CO and CO-CN poisoning

	CO	CO-CN
Fire smoke exposure	+/-	+
Soot in mouth or in airways	-	++
Gastrointestinal discomfort	++	-
Mental changes	+	++
Hypotension	+	++
Lactic acidosis	+/-	++

Notes: ++ characteristic, + present, +/- not characteristic, - absent

to have rapid antidotal activity and a favourable risk-benefit ratio also when used in the pre-hospital settings. Because of the lack of toxicity, hydroxocobalamin may be particularly useful for vulnerable populations such as paediatric patients.

- The use of dicobalt edetate is limited by its serious adverse effects, which include vomiting, urticaria, anaphylactic shock, hypotension and ventricular arrhythmias. No data regarding efficacy and safety are available for paediatric use.

Sodium thiosulfate (12.5 g i.v. over 10 min in adults and 400 mg/kg, up to a maximum of 12.5 g, in children) determines an enhancement of the transformation of cyanide in the less toxic thiocyanate. This mechanism is slower than that of cobalt compounds.*Botulism*

Botulinum neurotoxins (BoNTs, 15,000 Da polypeptide toxins) produced mainly by *Clostridia* species are the most potent identified natural toxins. These toxins may cause the potentially fatal neuro-paralytic syndrome defined “botulism”. Among the seven known neurotoxins (types A–G), the types A, B and E (rarely F) are toxic in humans, whereas type C and D cause disease mainly in animals, even if human cases have been reported. Recently, a chimeric BoNT type FA or HA (also called BoNT/H) was identified in a bivalent *Clostridium botulinum* Bh strain responsible for infant botulism, as well as a type X was identified in a *Clostridium botulinum* capable of producing type B toxin and isolated from an infant botulism case [25].

The toxins act specifically on neuromuscular junctions and cholinergic sites within the autonomic nervous system (all ganglionic synapses and post-ganglionic parasympathetic synapses) by binding to receptors located on the presynaptic membrane. After that, by endocytosis and through a complex process [involving Soluble *N*-ethylmaleimide-sensitive factor Attachment Protein Receptors (SNAREs) proteins], the toxin blocks the normal calcium-associated quantal release of acetylcholine from the presynaptic nerve terminals: this process is irreversible [26]. The toxic mechanism is quite similar for each type of BoNT and route of exposure, characterized

by a blockade of the voluntary motor and autonomic cholinergic junctions inducing an acute, afebrile, symmetric descending flaccid paralysis. The route of exposure influences the onset time of clinical manifestations, and consequently the delay from exposure to the appearance of typical syndrome.

Five well-defined forms of botulism are identified in relation to the route of exposure: foodborne, infant and adult intestinal, wound, iatrogenic and inhalation botulism [27, 28]. Some authors add a sixth form as botulism of unknown source [29]. All these forms are finally characterized by the same clinical syndrome. Foodborne botulism results from consumption of preformed BoNT complexes in food and is the most known and frequent form in Europe [27].

The **typical clinical syndrome is an acute (afebrile), symmetric descending flaccid paralysis** [30] that is

- characterized at ED presentation by some precocious signs/symptoms,
 - dysarthria (frequent),
 - rhinolalia,
 - dysphonia and dysphagia (as involvement of IX nerve).
- frequently associated with autonomic dysfunction (i.e. dry or sore mouth and throat) in patients with normal mental status and reflexes, without sensitivity disturbances
- and preceded by gastrointestinal discomfort (such as diarrhoea followed by constipation),
- and followed (in hours/days) by
 - diplopia blurred vision, mydriasis (often fixed), lateral rectus palsy and external ophthalmoplegia,
 - bilateral ptosis,
 - respiratory failure and hypotension and other autonomic instability [31].

The sensory system is not involved, as well as the intellectual functions. Clinical manifestations always begin in the bulbar musculature which is the most densely innervated and well vascularized (IX, X, XI and XII cranial nerves). These complaints are often underestimated; the first signs observed at clinical examination are

often those involving cranial trochlear (IV), abducens (VI) or oculomotor (III) nerves, with diplopia, blurred vision, mydriasis (often fixed), lateral rectus palsy and external ophthalmoplegia. Bilateral ptosis may be prominent. In severe cases the clinical features may worsen rapidly to respiratory failure (e.g. without gasping or agitation due to muscle paralysis) and, despite administration of supportive and specific therapy, mechanical ventilation is required. The period requiring mechanical ventilatory support ranges from 1 to 8 weeks, but patients can remain ventilator-dependent for 7–8 months: the average period for ventilatory support is 58 days for toxin type A and 26 days for type B [32]. After this, most patients have residual symptoms at 1-year follow-up, including easy fatigability, exertional dyspnoea [32], loss of responsiveness to postural change (orthostatic hypotension), hypothermia, alterations in the resting heart rate and urinary retention [33].

In severe cases, the prolonged extensive flaccid paralysis causes life-threatening complications: respiratory dysfunction may result from either upper airway obstruction (the weakened glottis tending to close during attempted inspiration) or diaphragmatic weakness. The most common complication in the first period of botulism poisoning is airways obstruction or aspiration pneumonia. Secondary medical complications from prolonged ventilator use, such as nosocomial infection, can occur.

Recovery results from new motor axon twigs that sprout and reinnervate paralysed muscle tissue in a process that may take months to complete [34]. The reported mortality rate is 25%, but most death occurred before 1980 (case fatality ratio was 40–60% during 1932–1979 vs 9% during 1980–2015) [35]. A correlation between fatal outcome and incubation period was found shorter in fatal group [1 day (range, 0.2–8 days) vs 1.5 days (range, 0.1–12 days)]. Excluding the cases of type F foodborne botulism, the highest percentage of patients with respiratory distress and mechanical ventilation support is in toxin type A group. The decline in mortality rate (for all toxin types) is due primarily to improvement in supportive and respiratory intensive care and perhaps to prompt administration of antitoxin [35].

Diagnosis

The unfamiliarity of clinicians with this rare poisoning may complicate the initial clinical suspicion. The **clinical syndrome** of botulism:

- Usually presents within 12 to 36–48 h after the ingestion of contaminated food; in some cases, however, onset of initial symptoms can be delayed as long as 10–15 days after the ingestion
 - The variability in the time of onset of symptoms depends on patient, type and quantity of toxin ingested and route of exposure and may make the diagnosis difficult
- The Autonomic symptoms, such as dry mouth or throat, may be the earliest clinical signs of poisoning, but they are frequently erroneously interpreted as pharyngitis
- It is easier to identify in case of cluster involving more than one case with coherent signs and symptoms
- It needs a specific treatment and a laboratory confirmation
 - Every case of botulism represents a potential public health emergency, and immediately, upon suspecting the diagnosis, the clinician should report the suspected case to the Ministry of Health or national agencies charged for this specific register.

Laboratory Diagnosis Confirmation

The diagnosis of botulism is essentially clinical, even if the role of the laboratory is mandatory in order (a) to confirm the clinical diagnosis, (b) to identify the different BoNTs involved, and (c) the source of poisoning.

Rapid and reliable analytical methods in biological samples are not normally available in the emergency field. The laboratory diagnosis of foodborne botulism is based on the following:

- The detection of BoNTs in clinical specimens or food samples
- The isolation of BoNT-producing clostridia from stools
 - The *in vivo* mouse lethality bioassay is the only standard validated method for the detection of BoNTs in food and in the patient's serum or stool [36]
 - A mouse type-specific botulinum antitoxin is used to define the type of the toxins produced from different strains
- To date, immunoassays for detecting BoNTs, assays for detecting catalytic activity of BoNTs, cell-based assays for detecting

biological activity of BoNTs and nucleic acid-based methods have been developed: some of these methods will replace the *in vivo* mouse lethality bioassay in the future.

Differential Diagnosis

Foodborne botulism poisoning is often underdiagnosed or misdiagnosed because physicians rarely encounter this disease; the initial symptoms can be confused. With more common clinical conditions, such as stroke, myasthenia gravis, the autoimmune acute demyelinating polyneuropathy known as Guillain-Barré syndrome (Miller Fisher variant), Eaton-Lambert syndrome, tick paralysis and shellfish or tetrodotoxin poisoning [34, 35]. As neurological syndrome; the absence of cranial nerves involvement at first stage of poisoning excludes botulism.

Key points to differentiate Miller Fisher syndrome (variant of Guillain-Barré syndrome) and botulism are reported in Table 18.13.

Treatment

The **treatment** of botulism includes procedures for decontamination, administration of antidotes and, when required, support of respiratory function. Only few differences are related to the way of exposure:

- In all cases of foodborne botulism, if no contraindications are present, gastrointestinal decontamination with cathartics should be considered with the aim of removing the spores and toxin from the gut. Conversely, gastric lavage or induced emesis is indicated only in asymptomatic patients that have very recently ingested a possible contaminated food
- Close monitoring of respiration is needed all throughout the disease as the high risk of rapid respiratory failure is the usual cause of early death in severe cases of botulism poisonings
- Antidotal treatment with botulism antitoxin has the aim of neutralizing the free circulating toxins still unbound to the nerve endings:
 - It should be administered as soon as botulism poisoning is suspected, before the laboratory confirmation

Table 18.13 Differential diagnosis between botulism and Miller Fisher syndrome and treatment

	Miller Fisher syndrome	Botulism
Positive history for infectious illness (e.g. flu-like syndrome)	Maybe	No
Oculobulbar symptoms	Present	Present (early stage)
Pupils	Normal	Mydriasis
Trend of neuroparalysis	Descending	Descending
Deep tendon reflex	Absent	Reduced or normal
Muscle coordination	Abnormal (ataxia)	Normal
Paraesthesia	Present	Absent
Symmetry of neurological manifestations	Yes	Yes
Dysautonomia	Present	Present
Electrophysiological tests (no pathognomonic pattern)	Normal motor and sensory conduction velocities with absent H reflexes, slowed nerve conduction velocities, reduced sensory nerve action potential amplitudes, or normal studies	Normal sensory nerve action potentials. Low-amplitude, short-duration and abundant motor-unit action potentials (BSAPs). Small evoked muscle action potential (MAP) in response to a single supramaximal nerve stimulus in a clinically affected muscle
Cerebrospinal fluid	Elevated protein levels (may be normal in early stage)	Normal
Treatment	Plasmapheresis or intravenous immunoglobulin	Antitoxin

- The antitoxin treatment limits the involvement of new nerve endings, and usually the clinical symptoms may progress for up to 12 h after antitoxin administration before an effect is observed [37]
- The type-specific antitoxins are ineffective against any other antigen
- The antitoxin is most often used for foodborne botulism, although it would be effective also in all the other forms, comprehending the inhalation of an aerosolized release of botulinum toxin (animal studies) [38, 39]
- Heptavalent Botulism Antitoxin (BAT) is the most available formulation in the world and treats all serotypes of BoNTs. It is an equine F(ab')₂ antibody that has to be administered intravenously at the recommended dose of one vial (20–50 ml) in adult patients. Skin sensitivity testing is optional, and a dosage adjustment (weight-based correction) is recommended in paediatric patients.

The disease is not contagious, and patients do not require isolation: only a hypothetical exposure originating from an aerial dispersion (e.g. terrorist attack) could potentially contaminate the non-exposed rescuers. In any cases, standard precautions should be exercised when evaluating and treating patients. Botulinum toxin cannot be absorbed through intact skin. Toxin can be absorbed through mucosal surfaces, eyes and non-intact skin. No case of person-to-person transmission of botulinum has ever been described, including in patient care settings. Nevertheless, persons exposed to bodily fluids or stool from patients with botulism should be advised of the early signs of botulism and should report for evaluation if these are noted. A first description of nosocomial transmission of *Clostridium butyricum* type E responsible for two cases of infant botulism has been recently described in two patients coming from different geographical areas [40]. This experience underlines the importance of applying the correct procedures to prevent nosocomial transmission of *Clostridium difficile* colitis and to reduce spreading of neurotoxins-producing clostridia spores [40].

NPS: New Psychoactive Substances

Recreational drug use remains common worldwide. Over the last decades, there has been a frenetic rush to the synthesis and marketing of new chemical compound that can be used as substitutes of the old/classic psychoactive drugs of abuse (e.g. cocaine, marijuana, heroin, amphetamines). These designer drugs are developed to provide rewarding effects similar to the old and illicit drugs of abuse while circumventing existing legislative classification and penalty. These compounds are generically called “novel” or “new” or “newer” psychoactive substances (NPS) and sometimes referred to as “legal highs”. The NPS are defined as “substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat” [41]. Until end of 2019, 119 countries and territories from all regions of the world reported one or more NPS.

The NPS include both medicine substitutes that can be bought without a medical prescription and recreational drugs that are sold freely, without any administrative or criminal consequences. The global trade in these molecules, often synthesized in hidden laboratories in a single country, is possible worldwide through Internet providers. Searching the Internet for these “designer drugs”, “legal highs”, “bath salts”, “spice”, “incense” and “research chemicals” today allows to easily buy hundreds of different molecules at low cost, very powerful, with a good degree of purity [42].

NPS are taken primarily for the effects on the CNS, but the toxic effects of these powerful molecules are not limited to the CNS but affect numerous various other organs and systems, including the heart. Similar to psychotropic medications, also the NPS act (although with different power for each molecule) on many receptor systems and ion channels that are widely represented and involved in the functioning of the CNS.

The wide range of newer illicit drugs presents today a challenge to physicians, especially in emergency settings. A general danger inherent in the use of illicit drugs is the lack of awareness of consumption:

in some cases, users consuming a different substance or a different “dose” from those they intended to take significantly increase the risk of accidental overdoses. As a result, the clinical picture can vary widely between patients even if they report using the same NPS. The poly-drug use is also extremely common, with alcohol, tobacco and marijuana that are frequently taken together with one or more NPS, with interactions that can be complex and unpredictable, and that can increase the risk of neurotoxicity.

NPS can be classified based on their chemical structure (synthetic cannabinoids, synthetic cathinones, ketamines, new phenethylamines, piperazines, tryptamines, synthetic opioids, etc.), mechanism of action and effects (stimulants, hallucinogenic, anaesthetic, dissociative, depressant, entactogen, etc.) (Table 18.14). Considering the number of the seized NPS, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) attributes to the synthetic cannabinoid receptor agonists (SCs) approximately the

Table 18.14 Summary of the toxic effects of the treated groups of new psychoactive substances (NPS)

Chemical class	Principal mechanism of toxicity	Major toxic effects
Synthetic cannabinoids	CB1 and CB2 receptor agonists displaying higher affinity, efficacy and potency compared to 19-THC	Euphoria, anxiolytic and antidepressant-like effects, paranoia, tachycardia, panic, convulsions, psychosis, visual/auditory hallucinations, vomiting and seizures
Synthetic cathinones	Sympathomimetic drugs that act on serotonin, dopamine and noradrenaline pathways	Agitation, restlessness, vertigo, abdominal pain, paranoia, rhabdomyolysis, convulsions and death
Arylcyclohexylamines	Dissociative anaesthetics that act as 5-HT2A agonist and NMDA receptor antagonist and show high affinity for opioid receptors	Distort perceptions of sight and sound, dissociation from the environment and self without hallucinations

Continued

Table 18.14 Continued

Chemical class	Principal mechanism of toxicity	Major toxic effects
Phenethylamines	Serotonergic receptor agonists that cause psychedelic effects and inhibit monoamine reuptake	Hypertension, vomiting, hyperthermia, convulsions, dissociation, hallucinations, respiratory deficits, liver and kidney failure and death in case of overdose
Piperazines	Stimulants that promote the release of dopamine and noradrenaline and inhibit the uptake of monoamines	Hyperthermia, convulsions and kidney failure; hallucinations and death have been reported at high doses
Tryptamines	5-HT _{2A} receptor agonists and serotonin reuptake inhibitors	Visual hallucinations, alterations in sensory perception, depersonalization
Opioids	Opioid receptor agonists/partial agonists, serotonin and or norepinephrine reuptake inhibition (tramadol, tapentadol)	Bradypnoea, apnoea, hypoxia, coma, noncardiogenic pulmonary oedema, seizures (codeine, dextromethorphan, meperidine, methadone, propoxyphene, tramadol), QT prolongation (methadone)

15–51% of the availability on the market, the 24–33% to the synthetic cathinones and the 17% to the new phenethylamines. Moreover, looking at the clinical effects that have been reported until December 2019 for NPS, the majority are due to stimulants (36%), followed by synthetic cannabinoid receptor agonists (30%), hallucinogens (15%), opioids (7%), sedative/hypnotics (3%) and dissociatives (3%) [43]. The new synthetic opioids, such as fentanyl and other molecules, have become the cause of enormous mortality and morbidity in the USA and in some European countries.

The number of NPS-related severe poisoning reported has grown parallel to the increasing number of new synthesized agents.

Several outbreaks occurred in USA and EU [44], with approximately 15% of cases admitted to intensive care units and some fatal cases [45].

The challenge to find out a pattern of intoxication and a compound-related risk, as well as specific treatments, is a difficult task due to the different diffusion across EU and USA, and the highly dynamic market. Moreover, only few people are aware of the specific substance that they have taken, and even rarer is the awareness of the potential side effects. Moreover, NPS intoxications are also often associated with the intake of the “oldest” drugs of abuse (such as THC, alcohol, cocaine, methamphetamine, MDMA). NPS are often supplied in a mixture of several agents, and frequently it is impossible to say which one on the market is the most powerful and most toxic.

Synthetic Cannabinoids/Synthetic Cannabinoid Receptor Agonists/CB1R “Super Agonists”

Synthetic cannabinoids (SCs) began to appear as drugs of abuse in Europe around the mid-2000s, initially as products commonly called “spice”. Since that time, their market has grown continuously, and SCs represent today the largest group (45%) of NPS monitored by the EMCDDA (Table 18.15). Those that have become available in recent years (e.g. MDMB-CHMICA, from 2014) are more powerful and more toxic than those initially placed on the market.

SCs compounds are CB1 receptor (CB1R) full agonists with higher potency as compared to THC: the affinity of JWH-018 for the CB1 receptor, for example, is five times as high as that of THC, while that of AM-694 is 500 times as high [46].

SCs exert a clinical THC-like effect, with alterations of mood, perception, sleep and wakefulness, body temperature and cardiovascular function. Their unwanted **side effects**, such as insomnia, memory impairment, headaches, dizziness and delusions, are more varied and more severe than those of THC.

The **acute toxicity of SCs** is not yet well defined, and clinical experiences confirm that acute toxic effects mimic sometimes those of

Table 18.15 Common name of representative compounds of NPS of the chemical group of SCs (non-exhaustive list)

Chemical group	Common names	
Naphthoylindoles	JWH-018 (spice)	JWH-122
	JWH-073	JWH-210
	JWH-022	WIN-55212-2
	JWH-081	AM-2201
	JWH-200	MAM-2201
		UR-144
Phenylacetylindoles	JWH-250	JWH-203
	JWH-251	
Benzoylindoles	WIN-48,098	AM-694
Cyclohexylphenols	CP 47497	HU-210
Indole and indazole	AB-PINACA	AB-CHMINACA
	ADB-PINACA	AMB-CHMICA
	5F-AB-PINACA	ADBICA
	5F-ADB-PINACA	5F-ADBICA
	AB-FUBINACA	BB-22
	ADB-FUBINACA	5F-PB-22 (AM-2201 carboxylate analogue quinolinyl derivative)

cocaine more than those of cannabis, including neuro-excitatory manifestations up to convulsions and serious cardiotoxic effects [47, 48]. CNS and cardiovascular toxic signs and symptoms are present in approximately 40–45% and 30–35% of cases, respectively. The ED presentation of SCs-intoxicated patients may include:

- Gastrointestinal symptoms: nausea, vomiting, hyperemesis, excessive sweating
- CNS toxic effects: anxiety, agitation, irritability, paranoia, hallucinations, delirium and toxic psychosis, aggressive and violent behaviour, cognitive deficits, memory loss, catatonia, seizures, coma or central nervous system depression
- Cardiovascular toxicity: arrhythmias (bradycardia or tachycardia), ventricular fibrillation, cardiogenic shock, myocardial infarction and/or cardiac arrest, subarachnoid haemorrhage and ischemic stroke are (reported also in paediatric patients) [49–51]

- Central respiratory depression
- Hyperthermia, rhabdomyolysis, liver toxicity and/or acute kidney failure [52]

The CB1Rs-stimulating substances (marijuana and SCs) are in fact responsible for vascular effect due to vasoconstriction such as in cases of transient ischemic events and strokes, even in young population (range 15–63). A recent review [53] evidenced 98 patients reported in the medical literature as having a cannabinoids-related stroke (85 after cannabis use and 13 after SCs). The type of stroke was an ischemic stroke and/or a transient ischemic attack, an haemorrhagic stroke, or an undetermined type of stroke in 85, 9 and 4 patients, respectively. Even if the prognosis was globally favourable (no or few sequelae) in 46% of cases, 5 patients died after the neurovascular event.

SC severe and fatal poisonings in young people are also frequent: the number of deaths reported in the medical literature appears to be increasing and mostly related to the use of the most recent and powerful SCs, such as 5F-ADB/FUB-AMB, 5F-PB-22 and AB-CHMINACA.

Prospective studies of cannabis users demonstrated increased risks of psychosis or psychotic symptoms with odds ratios ranging from 1.77 to 10.9. SCs have a greatly potential for inducing psychosis, and users (both frequent or even short or occasional user) can manifest delirium and persistent psychotic effects up to more than 40% of cases [44, 51].

The **diagnosis** is clinical and related to the history (if available), as SCs are usually undetectable on conventional toxicology testing in the hospital's emergency settings (they are detectable by second level toxicological laboratories).

The **treatment** is symptomatic (i.e. benzodiazepines, antipsychotics, anticonvulsant): ICU admission and mechanical ventilation for the wide range of SC toxic effects are needed in approximatively 60% of patients presenting in EDs. A 24–48 h ECG and cardiac enzymes monitoring is mandatory if patients present to EDs after use of SCs with cardiac signs/symptoms.

Synthetic Cathinones (β -Keto Amphetamines)

Synthetic cathinones (SCath) became widespread in early 2009; they are, by number of compounds under EMCDDA control, the second largest group of NPS abused in the EU (25–33%). All the synthetic cathinones are derivatives of cathinone, a naturally occurring stimulant found in the leaves of the khat plant (*Catha edulis*), the leaves of which are chewed in certain communities for their stimulant effects. More than 150 synthetic cathinones are available on the web market (Table 18.16).

SCath are generally falsely sold on the web market as “bath salts” or “plant fertilizers”, and they are insufflated (snorted), ingested or injected by users seeking psychostimulant effects similar to cocaine, ecstasy (MDMA) or other amphetamines.

The pharmacodynamic profile of cathinones is similar to that of other psychomotor stimulants. All the SCath show high blood-brain barrier permeability in in vitro models, with mephedrone and MDPV

Table 18.16 Common name of representative compounds of psychostimulant NPS of the chemical group of synthetic cathinones (non-exhaustive list)

Pentedrone	bk-2C-B	4-Ethylethcathinone (4-EEC)
Mephedrone	2,4-DMEC	4-Fluoroethcathinone (4-FEC)
Methylone (bk-MDMA)	α -PHiP	2-Fluoromethcathinone (2-FMC)
MDPV 3,4-methylene-dioxypyrovalerone	MDPHP	3-Methylmethcathinone (3-MMC)
Butylone (bk-MBDB)	4-MeO- α -PVP	4-MMC
Flephedrone (4-FMC)	N-Ethylheptedrone	4-EMC
Mexedrone	4-Fluoropentedrone	α -PVP
Naphyrone	4-Fluorocathinone	3F- α -PVP
Buphedrone	4F-buphedrone	4F- α -PHiP
Pentylone	N-Butylpentylone	2-MEC
Ephylone	bk-PMMA	3-MEC
		3,4-DMMC

that have particularly high permeability. The synthetic cathinones exert their action by increasing each one in different measure and proportion, the extracellular levels of norepinephrine (NE), dopamine (DA) and serotonin (5-HT) [54]. The users report euphoria, increased energy, loquacity, a subjective need to move and act, lightening of mood, empathy, openness, sexual stimulation and increased libido.

The **toxic effects** of synthetic cathinones are cardiovascular, neurological and psychiatric and are frequently indistinguishable from the acute effects of MDMA or cocaine. Intoxication is clinically characterized by:

- Gastrointestinal symptoms: nausea, abdominal pain
- Sympathomimetic effects: palpitations, tachycardia, hypertension, chest pain, ST-segment changes, breathlessness, peripheral vasoconstriction, mydriasis, myocarditis, cardiac arrest [55]
- CNS effects: anxiety, vertigo, impaired concentration and memory, headache, confusion, agitation, restlessness, paranoia, delirium, reduced level of consciousness, convulsions, syncope
- Serotonin syndrome
- Hyperthermia (up to 41.5 °C), elevated creatine kinase (CK) level and muscle damage, rhabdomyolysis, metabolic acidosis
- Psychotic manifestations that often consist of paranoia with auditory and visual hallucinations, which can persist for up to 4 weeks and take a more severe course than with amphetamines. Several cases of SCath intoxication with psychotic symptoms are related to MDPV [56]

Symptoms may persist for 24–48 hours in 45% of cases, and neurological and cardiovascular symptoms can be long-lasting. There have been several reports of serious toxicity associated with synthetic cathinones, including many fatalities in EU, the USA and Japan: cardiac ischemia and heart failure can be the most plausible cause of death [57]. Cardiac toxicity and death have been reported also to be related to the QT prolongation and the consequent torsade de pointes [58]. Severe reversible cardiomyopathy has been reported following use of “bath salts” containing mephedrone and MDPV.

The **diagnosis** is prevalently clinical and related to the history (if available): SCath are usually undetectable on conventional

toxicology testing in the hospital's emergency settings. Synthetic cathinones can be detected in serum by second level toxicological laboratories for 15–48 h after use [59]. The treatment is symptomatic, as no specific antidotes are available for the treatment of these intoxications.

Ketamine and Ketamine Derivatives (Arycyclohexylamines)

The dissociative narcotic and anaesthetic drug ketamine (KET), frequently used as NPS, is structurally and toxicologically similar to the new NPS compound methoxetamine (MXE) and to phencyclidine (PCP). Several other arycyclohexylamines are available for abuse on the web market (Table 18.17).

The users develop multimodal hallucinations, floating sensations, paranoia, dissociation, nightmares, reduction or loss of motor activity and changes in sexual and musical perceptions. Tolerance, dependence, flashbacks and withdrawal symptoms are frequent.

CNS effects of ketamine are the result of complex dose- and time-dependent interactions on many types of receptors on which these substances exert agonist (glutamate, acetylcholine) or antagonist (NMDA) effects, direct or indirect (e.g. disinhibition of glutamatergic activity, activation of dopamine transmission, 5-HT release), which can also be different in different brain areas. Several toxic effects are reported also on the bladder, kidney, adrenal gland, pancreas and intestinal tract.

MXE acts through blockade of the NMDA receptor and dopamine reuptake: other mechanisms not fully elucidated are the agonist effect on D₂ dopaminergic receptors and the interaction with

Table 18.17 Common name of representative compounds of the dissociative NPS arylcyclohexylamines (non-exhaustive list)

Keta	3-MeO-PCP
MXE, methoxetamine	4-MeO-PCP
Deschloroketamine	3-MeO-PCE
Methoxpropamine	2-Fluorodeschloroketamine
Deschloroketamine	

serotonergic 5-HT₂ receptors, opioids (μ , κ), σ receptors and muscarinic cholinergic receptors [60, 61].

KET and MXE recreational uses cause euphoria, increased empathy, intensified sensory experiences, distortion of the sense of reality and of time, vivid and persistent visual hallucinations, paranoia and anxiety. These are associated with effects (sometimes called “not sought”) such as sensory deprivation, derealization and dissociation (generally described as “near-death experience”).

KET and MXE are the most frequent NPS involved in severe intoxication in many countries. They have relevant psychotropic effects, and their use cause severe psychiatric diseases.

The **intoxication** is characterized by:

- Nausea, vomiting, diarrhoea
- Hallucinations, agitation, violent behaviour, severe psychomotor agitation, paranoia, catatonia, mental confusion, dizziness, aphasia, synesthesia
- Respiratory depression
- Mydriasis, tachycardia, hypertension, palpitations and chest pain [62].

Isolated reports describe also withdrawal-like symptoms such as insomnia, deflection of mood and post-intake depressive states.

The **treatment** in EDs is based on rapid benzodiazepine administration and all the needed symptomatic treatments.

NPS Psychostimulants

All the NPS psychostimulants inhibit, even if in different degree related to the specific compound, the monoamine reuptake increasing the quantity of noradrenaline, dopamine and serotonin in the synaptic cleft, leading to sympathomimetic effects that are responsible for most of the toxic effects. The NPS with dominant psychostimulant effects, also called entactogens, are generally sold on the market as “party pills” that enhance feelings of empathy and emotional closeness to others. Most of them are the novel substitutes of the old drug of abuse ecstasy (MDMA).

Toxic effects may vary between each class and each compound:

- Agitation and euphoria are common features after use of all these substances
- Cardiovascular effects include tachycardia, hypertension, vasoconstriction of coronary arteries, chest pain (due to an increase in oxygen demand), thrombosis and increased risk of myocardial infarction and stroke: dilated cardiomyopathy is related to prolonged abuse. Acute coronary syndrome with fatal outcomes has been reported [63]
- Hyperthermia (serotonin toxicity) and dehydration are observed.

Phenethylamine-derived compounds comprehend a vast number of NPS (new amphetamine derivatives, piperazines, tryptamines, piperidols/piperidines, aminoindanes, benzofurans and others) that have **dominant psychostimulant and/or hallucinogenic effects**, in part predictable based on their chemical structure (Table 18.18). However, from the clinical point of view, it is very difficult to identify the involved compound based only on the signs and symptoms, both for the different individual response to each agent and for the modification of the effects with the increase of the taken dose. Moreover, most compounds have a combination of such effects.

The **treatment** is similar to that of amphetamines or cocaine overdose. The initial treatment should be with benzodiazepines, eventually associated with nitrates for the cardiotoxic effects. Conversely, β -blockers should be avoided, because β -blockade will potentially leave α_1 -receptors unopposed resulting in more severe coronary spasm or arterial blood pressure increase. Concerning the sodium channel blockage, in case of QRS widening and consequent risk of dysrhythmias, sodium bicarbonate should be used as the first-line treatment.

Serotonin toxicity (CNS activation, autonomic dysregulation and neuromuscular impairment) could also be present, as many compounds share serotonergic properties. The SIADH syndrome (inappropriate antidiuretic hormone secretion) resulting in hyponatremia has been also reported [64]. Extensive cooling is needed in case of hyperthermia, whereas first-line treatment of serotonergic symptoms is benzodiazepines, followed by cyproheptadine.

Table 18.18 Representative compounds of NPS with predominant psychostimulant effects belonging to the chemical groups of the new phenethylamines/amphetamines, piperazines, aminoindanes, benzofurans and piperidine/pyrrolidines (non-exhaustive list)

Chemical group	Common names	
New amphetamine derivatives	PMMA	2-FMA
	PMA	2-PEA
	4-FMA	DMMA
	4-CA	DMA
	2-FA	Beta-Me-PEA2
	4-FA	Phenpromethamine
Piperazines	BZP	2C-B-BZP
	DBZP	TFMPP
	pCPP	pMeOPP
	mCPP	pFPP
Aminoindanes	1-Aminoindan	MMDAI
	2-Aminoindan	MDAT
	5-IAI	<i>N</i> -Methyl-2AI
	MDAI	
Benzofurans and benzodifurans or arylalkylamines	5-APB	6-APB
	5-APDB	6-APDB
	2C-B-Fly	Bromo-Dragonfly
Piperidines/pyrrolidines	2-DPMP	Isopropylphenidate
	Desoxy-D2PM	4-F-Methylphenidate (4F-MPH)
	Ethylphenidate	

The new synthetic amphetamine derivatives group show clinical effects almost completely superimposable to those of the classic amphetamines [65]. The **intoxicated patients** presenting to the ED show:

- Agitation, hallucinations, seizures (34% of patients)
- Severe tachycardia (64% of cases), hypertension, elevated heart and respiratory rate, mydriasis, severe limb ischemia
- Liver and renal failure
- Severe hyperthermia (36% of cases).

A high number of fatalities are reported in PMA and PMMA users, frequently related to multiple organ failure. A case series of 33 intoxicated patients with 4-FA (4-fluoroamphetamine) showed that 8 had important complications, including 2 deaths, 4 cerebral haemorrhages, 2 instances of Takotsubo's cardiomyopathy, 1 myocardial infarction and 1 acute heart failure [66].

Piperazines (1-benzylpiperazines—BZP and 1-phenylpiperazines) enhance the release of dopamine and norepinephrine and inhibit the uptake of dopamine, norepinephrine and serotonin, increasing activation of both central and peripheral α - and β -adrenergic post-synaptic receptors. High doses of BZP are usually associated with a **sympathomimetic toxidrome and paranoid psychosis**: palpitations, tachycardia, agitation, anxiety, confusion, dizziness, headache, tremor, mydriasis, insomnia, urine retention and vomiting. Seizures are present in some patients even at low doses. Severe multiorgan failure, QT prolongation, hallucinations and metabolic acidosis have been reported. A case series of 178 patients admitted to EDs had long-lasting (more than 24 h) effects, comprehending extreme hyperthermia ($>40^\circ\text{C}$) and multiorgan failure, palpitations, tachycardia, seizures, metabolic acidosis and hyponatremia [67].

Benzofurans (APB, APDB) are deoxygenated derivatives of MDA (methylenedioxyamphetamine) with agonist action on 5-HT_{2C} receptors. The benzodifurans bromo-dragonfly and 2C-B-Fly are likely to act as catecholamine-releasing or reuptake-inhibiting agents. Both are potent 5-HT_{2A} agonists, but they are also both 5-HT_{2B} and 5-HT_{2C} agonists.

The effects of using 6-APB are similar to, but much more intense than, those resulting from taking MDMA: in some case hallucinogenic effects last 2–3 days. Acute **intoxication** manifests with:

- Gastrointestinal symptoms (nausea and vomiting)
- Prolonged sympathomimetic effect on the heart (severe tachycardia, hypertension)
- Hyperthermia, rhabdomyolysis, pronounced mydriasis
- Severe psychomotor agitation, violent attitude, auditory/visual hallucinations and sensory disturbances and convulsions [68].

Several deaths and severe peripheral vasoconstrictions are described in patients with bromo-dragonfly intoxication in USA and EU [69].

Sudden deaths apparently result from a severe and prolonged arteriolar and coronary vasoconstriction due to the potent agonism at both the 5-HT₂ and α-adreno-receptors, which may persist for days.

Large doses of **benzodiazepines**, **vasodilators** (nitrates, nitropruside) and **calcium-channel blockers** have been used to counteract the severe vasospasm and the neuropsychiatric and cardiac sign and symptoms.

New Hallucinogen Phenethylamine- and Tryptamine-Derived Drugs

In Europe, the EMCDDA reports an increase in the consumption of phenethylamines associated with severe acute poisoning and deaths. Most new phenethylamines have stimulant properties: depending on the “designer” chemical modification, stimulant or hallucinogenic properties are conferred to the new compounds. The principal substituted phenethylamines subgroups are the 2C agents, 2D agents and NBOMe agents (Table 18.19). Another group of hallucinogenic compounds is represented by the synthetic tryptamines (Table 18.20).

Table 18.19 Representative compounds of predominant hallucinogen NPS belonging to the agents-substituted phenethylamines subgroups (non-exhaustive list)

Chemical group	Common names	
2C agents-substituted	2C-T-2	2C-H
	2C-P	2C-B
	2C-I	2C-E
	4C-D	2C-N
	2C-D	2C-G
2D agents-substituted	DOI	DOM
	DOC	DOF
	DOB	
NBOMe agents-substituted	25H-NBOMe	25G-NBOMe
	25I-NBOMe	25D-NBOMe
	25B-NBOMe	25C-NBOMe
	25E-NBOMe	25I-NB4OMe
	25N-NBOMe	30C-NBOMe

Table 18.20 Representative compounds of hallucinogen NPS belonging to the chemical groups of synthetic tryptamines (non-exhaustive list)

Chemical group	Common names	
Synthetic tryptamines	AMT	4-HO-MET
	5-IT, 5-API	4-AcO-MET
	5-APDI	4-AcO-MPT
	4-AcO-DPT	MIPT
	5-MeO-DPT	DMT
	4-AcO-DMT	5-MeO-tryptamine
	4-AcO-DALT	DALT
	5-MeO-AMT	4-AcO-DALT
	5-MeO-DMT	5-Meo-DALT
	4-AcO-DET	DPT

Phenethylamines of the 2C-series have affinity for both 5-HT₂ receptors and alpha-adrenergic receptors. They have a prevalent effect of inhibition of monoamine reuptake (mainly serotonin and noradrenaline) and can exert also important postsynaptic direct effects. These compounds can carry out agonist or antagonist activity in relation to the involved receptor subtypes [70]. Clinically, the 2C-series are primarily **stimulant** at lower doses (e.g. 10 mg for 2C-B), but doses of more than 10 mg tend to be psychoactive with **hallucinogenic and entactogenic effects**, while doses of 30 mg or more may cause **intense hallucinations or psychosis**. Deaths have been associated with the 2C-series agents.

The psychedelic phenylethylamine derivative **2C-B**, currently sold as a substitute for MDMA, is a partial agonist on the serotonin receptor subtypes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. **Acute intoxications** are characterized by vomiting, seizures, coma, mydriasis, tachypnoea, hypertension, tachycardia, metabolic acidosis and a constellation of psychedelic/psychostimulant effects like those associated with serotonin-acting drugs.

2C-E agents are sold as “mescaline” for their predominantly hallucinatory effects. **Intoxicated patients** present with delirium, hallucinations, psychomotor agitation, euphoria, paranoid delusions,

persistent acute psychosis, violent attitude, hyperactivity (sometimes defined as “excited delirium syndrome”) [71], hyperthermia, potentiation and distortion of sensations (tactile, auditory and olfactory), nausea, vomiting, tachycardia, hypertension, hypoxia, tachypnoea and convulsions. 2-CE fatalities have been reported, and a lethal toxic leukoencephalopathy related to assumption of 2C-E compounds has also been described in a psychiatric patient [72].

Similarly, **2C-I acute intoxications** are characterized by tachycardia, severe systolic hypertension (greater than 220–235 mmHg), hyperthermia, severe psychomotor agitation, seizures, spontaneous clonus, hypertonia, muscle stiffness, delirium, coma and reduction of oxygen saturation [73]. Some symptoms are compatible with severe serotonin syndrome, and in these cases, benzodiazepines, fentanyl, phenobarbital, cyproheptadine, propofol, intubation and assisted ventilation can be needed [74]. Some cases of intoxication have had lethal outcome.

The **2D-series or D-series** agents are potent 5-HT₂ receptor agonists and full agonist at 5-HT_{2A} and 5-HT_{2C} subtypes, producing potent hallucinogenic effects, prolonged vasoconstriction and dopaminergic agonism. Severe hallucinations, extreme dysphoria, sensation of limb and generalized body pain, agitation and vomiting are the user’s reported effects. In cases of **intoxication**, the potent hallucinogenic effect can last more than 24 h, accompanied by vasospasm in upper and lower extremities, hypertension, convulsion, tachycardia, mydriasis and coma [75]. The treatment requires phentolamine and/or nitroprusside administration: fatalities are reported.

Tens of **NBOMe** are reported today in the EMCDDA database. They are sold as “blotter”, “trip”, “smiles”, “N-bomb”, “LSD”, “new LSD”, “synthetic LSD”, “synthetic speed”, “25L”, “25B”, “25C” or with other slang terms. They are very powerful compounds, at least as much as LSD. Acute NBOMe **intoxications** are characterized by important and prolonged **hallucinations, violent agitation, mental confusion, a state of great concern with anxiety and self-injurious gestures**: accompanying symptoms are mydriasis, tachycardia, hypertension, hyperthermia, sweating, hyperreflexia, muscle

hypertonicity, convulsions, rhabdomyolysis and kidney damage (partly attributable to powerful serotonergic stimulation). Several dozens of cases of severe and lethal intoxication are reported to date in the medical literature: the lethality turns out to be 15% of the reported cases and the need of ICU admission 40% of the cases [76]. The presence of hallucinations, self-injurious gestures and state of severe agitation is the most evident clinical feature of NBOMe intoxications. Consequently, most cases of serious injury and death in NBOMe series-intoxicated patients are due to self-injurious acts and/or reckless gestures (e.g. throwing themselves thinking of flying) in people who lose control of themselves. The initial **therapeutic** approach of these cases of intoxication is in fact precisely aimed at the important and rapid sedation of the patient to prevent other damage from being caused; in fact, often these patients come to the observation of emergency medical services following (unconscious) gestures of self-harm.

Synthetic tryptamines. The natural occurring tryptamines and ergolines have been used for centuries as psychoactive substances obtained from ayahuasca (DMT, dimethyltryptamine), mushrooms (psilocybin, psilocin) and plants (e.g. ergine, mitragynine); LSD (lysergic acid diethylamide), on the other hand, is the best-known synthetic tryptamine and one of the most potent hallucinogens. The new synthetic tryptamines (e.g. 5-MeO-AMT, 5-MeO-DMT) (Table 18.7) act both as 5-HT_{2A} and 5-HT_{1A} receptor agonists and serotonin reuptake inhibitors, provoking visual hallucinations, alterations in sensory perception and depersonalization [77]. **Intoxicated** patients present to EDs with **hallucination, paranoia, agitation, mydriasis, severe tachycardia, arrhythmias, hypertension, hyperthermia and diaphoresis**: metabolic acidosis, rhabdomyolysis and renal impairment can be present. Deaths are reported.

Peripheral Neurotoxic Syndromes

Many agents determine peripheral neurotoxicity (Table 18.21): as examples, a metal toxic effect and two different intoxications due to natural toxins are reported in this paragraph.

Table 18.21 Selected agents that cause peripheral neuropathy

Agent	Neuropathy/other information
Acrylamide	Sensory and motor distal axonal neuropathy
Amiodarone	Peripheral demyelination
Antineoplastic agents	Vincristine most strongly associated
Antiretroviral agents	Nucleoside reverse transcriptase inhibitors
Arsenic	Sensory-predominant mixed axonal neuropathy
Buckthorn (<i>Karwinskia humboldtiana</i>)	Livestock and human demyelinating neuropathy
Botulism	See specific paragraph
Carbon disulphide	Sensory and motor distal axonal neuropathy
Carbon monoxide	Possible sequelae
Ciguatoxin	Axonal neuropathy, potentially reversible
Colchicine	Sensory neuropathy and preservation of reflexes
Dimethylaminopropionitrile	Urogenital and distal sensory neuropathy
Disulfiram	Sensory and motor distal axonal neuropathy
Doxorubicin	After liposomal doxorubicin
Ethanol	Sensory and motor distal axonal neuropathy
<i>n</i> -Hexane	Sensory and motor distal axonal neuropathy
2,5-Hexanedione and methyl <i>n</i> -butyl ketone	Sensory and motor distal axonal neuropathy
Hydrofluoric acid	Sensory distal neuropathy (related to site of exposure)
Isoniazid	Preventable with co-administration of pyridoxine
Lead	Motor-predominant mixed axonal neuropathy
Mercury	Organic mercury compounds

Continued

Table 18.21 Continued

Agent	Neuropathy/other information
Nitrofurantoin	Sensory and motor distal axonal neuropathy
Nitrous oxide	Sensory axonal neuropathy with loss of proprioception
Organophosphate insecticides	Specific agents only (e.g. triorthocresyl phosphate)
Platinum-containing antineoplastics	Sensory neuropathy
Selenium	Polyneuritis
Tacrolimus	Peripheral demyelination
Thallium	Sensory and motor distal axonal neuropathy
Tick paralysis	Ascending flaccid paralysis after bites by several tick species
Vinca alkaloids	As antineoplastic agents, vincristine

Chemical toxins cause also cranial nerve neuropathies that can be considered in the differential diagnosis of many other diseases (examples in Table 18.22): usually, the bilateral involvement of the cranial nerves can be a good index of the toxicological nature of the neuropathy.

Thallium

Thallium chemical properties make its salts highly toxic because they are tasteless, odourless, completely water soluble and rapidly adsorbed by the gastrointestinal tract. This metal is difficult to find and, due to toxic effects, is strictly limited to the public [78]. Despite the limitations, thallium causes accidental or intentional poisonings (criminal acts) characterized by atypical clinical presentation during early stage of poisoning which often leads to a missed diagnosis. The minimum lethal dose of thallium salts is 15 mg/kg [79].

Thallium, a univalent cation similar to potassium, interferes with potassium-dependent pathways and finally causes cell death.

Table 18.22 Examples of cranial nerve neuropathies related to toxic agents

Agents	Sign/symptoms	Cranial nerve
Methanol	Blindness and pupil unresponsive to light	II
Botulinum toxin	Ptosis, pupils unresponsive to light, photophobia	III
	Paralysis of the superior oblique muscle of the eye, vertical and torsional diplopia	IV
	Paraesthesias of the face, weakness in chewing	V
	Impaired taste and gag reflex	IX
	Change in voice, decreased gag reflex	X
	Weakness neck/shoulders	XI
	Tongue deviation, impaired speech, dysarthria	XII
Thallium	Ptosis, pupils unresponsive to light, photophobia	III
	Paralysis of the superior oblique muscle of eye, vertical and torsional diplopia	IV
	Failure to abduct eye, diplopia	VI
Antimuscarinics	Ptosis, pupils unresponsive to light, photophobia	III
Tetanus toxin, strychnine	Hypercontractility and trismus	V

Thallium is distributed in all body tissues, and it is characterized by active enterohepatic circulation determining the faecal route as primary elimination.

Toxic effects of thallium are related to the absorbed dose and to the modality of exposure (single, repeated, chronic exposure):

- At the early stage of poisoning (first 2–4 days), the patient may present mild gastrointestinal discomfort including abdominal pain, vomiting, diarrhoea or constipation associated with severe asthenia, diffuse myalgia, chest pain, non-specific ST-T changes and (rarely) insomnia or hallucinations. If history of thallium exposure is negative and if there are no other patients involved—linked to the index case—the

clinical suspicion is very difficult. Typically, the patient has multiple successive accesses to the ED [80]

- Pathognomonic syndrome involves mainly the peripheral nervous system
 - Rapidly progressive painful paraesthesia and peripheral neuropathy starting from feet and legs
 - Respiratory failure necessitating respiratory support present in severe cases
- The typical alopecia appears around 1–2 weeks after exposure; at the fourth week, a near-total-body alopecia (including axillary and pubic hair) is documented. Sometimes nail dystrophy (Mees lines) may also appear.

The **diagnosis** of this rare poisoning is very difficult. The early recognition of poisoning permits to start the specific treatment as soon as possible. The identification of toxic concentrations of thallium in blood, urine or hair confirms the diagnosis. Electrophysiological tests are useful in diagnosis of sensorimotor axonopathy and in monitoring the clinical evolution. Thallium is radiopaque, and abdominal radiograph may be used to quantify the material in the gastrointestinal tract.

The treatment includes:

- Gastric lavage in case of recent and massive ingestion
- To prevent toxic effects and to increase the elimination of thallium, the antidote Prussian blue (ferric ferrocyanide—500 mg tablets) must be administered (adult: 3 g orally three times per day). Prussian blue acts as exchanger of potassium for thallium in the gut, resulting in an increased faecal elimination of thallium-Prussian blue complex [81, 82]
- Forced diuresis, dialysis or hemoperfusion is not indicated for thallium removal.

Thallium toxicosis should be considered when gastrointestinal discomfort and painful paraesthesia are followed by alopecia.

Tetanus

Tetanus is a rare disease in developed countries and is characterized by uncontrolled, severe contractions of voluntary skeletal muscle possibly associated with generalized tonic activity (opisthotonos) [83]. The first sign is lockjaw, or trismus, or “*risus sardonius*”, due to a severe muscular contraction of the face including masseters. In severe cases respiratory failure and death may occur. Several forms of tetanus have been described: generalized (80% of all cases), local, cephalic and neonatal [84]. Tetanus is caused by an exotoxin (tetanospasmin) produced by *Clostridium tetani* (anaerobic spore-forming, gram-positive rod found widely in soil and in the gastrointestinal tract). Tetanospasmin (150 kDa peptide) prevents the release of inhibitory neurotransmitters in the CNS: the loss of inhibitory transmission results in severe muscle spasms [85]. Typically, the incubation period between primary wound and clinical manifestations is 1–2 weeks. In some cases (up to 10%), the initial wound is not detectable at the stage of evident intoxication. Despite the advanced treatment, the mortality remains high.

The **diagnosis** of tetanus is essentially clinical: **pathognomonic are the muscle spasms in awake patient with (possibly) a wound and an incomplete immunization history**. Specific toxin assays useful in emergency settings are under investigation, and serum antibody level quantification—up to 0.16 IU/ml—is related with prior immunity.

Differential diagnosis includes strychnine poisoning, severe hypocalcaemia, neuroleptic malignant syndrome and dystonic reactions [86].

Treatment is based on symptomatic treatment, supportive care, wound care associated with antibiotic treatment and toxin neutralization [87].

- Muscle relaxants and sedatives are the mainstay of symptomatic treatment of tetanus and include the administration of diazepam (0.1–0.2 mg/kg i.v.) or midazolam (0.05–0.1 mg/kg i.v.)

associated with morphine to treat pain. In some cases, a dose of 3400 mg of diazepam and 1440 mg of midazolam over 24 h period were administered to counteract muscle spasms [86]. In severe cases, non-depolarizing neuromuscular blocker (e.g. rocuronium or vecuronium) has been administered to obtain complete neuromuscular paralysis, obviously associated with endotracheal intubation and assisted ventilation.

- Baclofen is a GABA-B receptor agonist. Oral baclofen is thought to have poor penetration across the blood-brain barrier, and hence it is ineffective in tetanus. However, intrathecal administration is shown to abolish spasms promptly. Its use is limited due to costs and the risks of introducing concurrent central nervous system infection. Baclofen administration should be considered in severe cases unresponsive to benzodiazepines treatment [86].
- Benefits reported with dantrolene and botulinum toxin (for local forms of spasms) in reducing muscle spasms, such as that of epidural blockade and clonidine to reduce autonomic dysfunction, need to be further evaluated with controlled trials before being recommended as standard treatments.
- Debridement of the identified wound is extremely important to limit the severity of the intoxication; clostridiocidal antimicrobial treatment with metronidazole is strictly indicated.
- Magnesium sulphate acts as a physiological antagonist of calcium at the cellular level causing vasodilatation, presynaptic neuromuscular blockade and prevention of catecholamine release. It also has anticonvulsant properties. Magnesium treatment to control tetanic spasms has been established since the 1980s, when successful control of tetanic spasms with continuous infusions was reported. A safe serum therapeutic range of 2–4 mmol/l has been established [88].
- Human tetanus immunoglobulins (HTIg) neutralize circulating toxin but has no effects on toxin already bound to neurons. The administration is indicated as soon as possible and when the clinical suspicion is made. The recommended dose of HTIg varies from 500 to 6000 IU, intramuscular. Usually a dose of 3000–5000 IU for children and adult is indicated. The half-life of HTIg is 25 days.

- Theoretically, intrathecal HTIg could potentially bind the toxin during its transfer from the postsynaptic terminal to the pre-synaptic level. Intrathecal administration of immunoglobulins (in addition to intramuscular administration) may be beneficial.

Vaccination is effective in preventing this severe intoxication.

Ciguatoxin

Ciguatera fish poisoning (CFP) is due to the consumption of “toxic” coral reef fish from tropical or subtropical areas contaminated by ciguatoxins (CTXs). CTXs are a family of neurotoxins produced by a dinoflagellate belonging to *Gambierdiscus* genus [89, 90]. To date, CFP is endemic in Caribbean, Indo-Pacific Islands, Indian Ocean and French Polynesia [91, 92]. However, recent indigenous CFP cases have been described in Spain (Canary Islands), and CTXs-containing marine organisms have been identified in the Madeira archipelago and Israeli coast underlying a recent expansion of CTXs at a globe scale [93]. Moreover, due to globalization, tourism and interest for exotic products, non-endemic regions, such as Europe or North America, assist to the increase of imported CFP cases that raises “new” concerns about medical approach and management of this “new” poisoning [94].

CTXs are potent (active at nano- or pico-molar concentrations) highly lipophilic polyether that bound voltage-dependent sodium channels and are responsible for significant excitable cell disturbances. Ciguatoxin stabilizes the open state of the sodium channel and causes persistent depolarization.

The **diagnosis** is difficult to establish, especially in non-endemic region. Common signs and symptoms include:

- Gastrointestinal effects (abdominal pain, vomiting and severe diarrhoea) that generally appear within 12 hours and resolve after 24–48 hours.
- Hypotension, electrolyte abnormalities and acid-base alterations (and rarely bradycardia) are suggestive of the severity of the poisoning

- Other initial symptoms may include a severe asthenia, general malaise, hiccup, pain and weakness of lower limbs, extreme pruritus (without cutaneous signs), arthralgia and paraesthesia (typically perioral and at the extremities). All this constellation of clinical manifestations appears in an afebrile patient. Pathognomonic is the dysesthesia in response to cold stimulations, named also “temperature reversal” or (more correctly) “cold allodynia”
- Severe asthenia is common in patients for months after the acute phase [95].

The mortality rate is lower. Chronic form of CFP is usually defined as the persistence of symptoms for more than 2–6 months; the prevalence of chronic CFP is up to 20%. Some patient may present a reactivation of the poisoning after a variable asymptomatic free time. Chronic CFP manifestations are mainly neurologic such as paraesthesia, dysesthesia, cold allodynia, itching, headache, cognitive dysfunction, sleep disorder, anxiety, memory loss, depression and systemic (i.e. myalgia, severe asthenia and arthralgia).

Clinical suspicion is possible when history is positive for saltwater (marine) fish consumption (that has been previously associated with CFP) and patient reports neurologic symptoms which may include any combination and sequence of paraesthesia, dysesthesia, pruritus, allodynia, myalgia, arthralgia and dizziness with onset up to approximately 48 h after eating the fish. Gastrointestinal symptoms often precede or accompany the neurological symptoms. The only way to confirm the poisoning is the detection of ciguatoxin(s) in implicated raw or cooked fish meal remnant. Additional item for clinical suspicion is the epidemiological criteria.

Electrophysiological test may help for differential diagnosis. Quantitative sensory test (QST) consisting in thermal stimulations (warm and cold stimuli through a Peltier-based contact thermode) is indicated to quantify the sensory disturbance.

Unfortunately, no specific antidote is available, and many agents were tried with little good evidence. The treatment comprehends:

- Activated charcoal administration if the ingestion of ciguateric fish is recent
- Symptomatic treatment is indicated (intravenous fluids)
- Atropine should be considered in case of bradycardia (rarely)
- Amitriptyline should be considered for pruritus or headaches
- Gabapentin or pregabalin is used for paraesthesia
- Early intravenous administration (within 72 h from poisoning) of repeated high doses of mannitol (1 g/kg over 30 min) may reverse the effects of CTX by inhibiting ciguatoxin-induced opening of sodium channels, by reducing—as osmotic action—the neuronal oedema and the cellular excitability
 - Mannitol has been administered also in patients presented with chronic ciguatera with positive clinical response also up to several weeks or months after exposure.

In conclusion, it is reasonable to consider using intravenous mannitol in cases of acute ciguatera fish poisoning [96]. Medications used in other neuropathic syndromes appear to suppress the paraesthesia in persistent ciguatera cases. However, the human evidence is of low quality for all medical treatments.

Neurotoxic Adverse Drug Reactions

Serotonin Toxicity

The term “serotonin toxicity” defines a series of clinical manifestations that can be caused by numerous substances or compounds capable, at various levels, of increasing serotonergic stimulation. Since the signs and symptoms can present with different intensity, it is currently preferred to speak of “serotonergic toxicity” rather than “serotonergic syndrome”.

Symptoms may appear during treatments or in case of acute overdoses [97]. The most serious clinical manifestations are often related to drug-drug interactions, especially in high-dose treatments [98].

Serotonin toxicity can be caused by a wide range of different drugs and by different drug combinations [99], with the final common route believed to result in a marked increase in serotonergic neurotransmission. **Drug and substances implicated can be divided into:**

- Serotonin precursors (e.g. dietary tryptophan supplements)
- Enhancers of serotonin release:
 - Drugs of abuse: cocaine, MDMA ("ecstasy")
 - Amphetamine and derivatives
 - Dextromethorphan
- Direct serotonin receptor agonists:
 - Triptans (e.g. almotriptan, rizatriptan, sumatriptan)
 - Ergot derivatives (ergotamine and methylergonovine)
 - Opiates (fentanyl, meperidine)
 - Drugs of abuse: LSD
 - Antidepressants/mood stabilizers (mirtazapine, trazodone, lithium)
- Inhibitors of serotonin reuptake:
 - SSRIs, SNRIs antidepressant (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, duloxetine)
 - Amphetamine and derivatives
 - Cocaine and MDMA ("ecstasy")
 - Tricyclic antidepressant (e.g. amitriptyline, clomipramine, imipramine)
 - Opioids (include dextromethorphan, meperidine, methadone, pentazocine, pethidine, tapentadol, tramadol)
- 5-HT₃ receptor antagonists:
 - Ondansetron and granisetron
 - Antihistamines: chlorphenamine
 - Herbal supplements: St. John's wort (*Hypericum perforatum*)
- Inhibitors of serotonin metabolism:
 - MAOIs (selegiline, linezolid, methylene blue, St. John's wort)
- Drugs that sensitize serotonin receptors:
 - Second-generation antipsychotics (e.g. quetiapine, risperidone, olanzapine, clozapine, aripiprazole)

Clinical Picture and Diagnostic Criteria

The presentation is highly variable ranging from mild symptoms to a severe life-threatening syndrome (Table 18.23). The onset is rapid, within a few hours from the change in the drug taken or after an acute overdose. In the same way, the resolution of the picture generally takes place in a few hours (even if it can last beyond 48 h for the most serious forms) from the suspension of the causative agent and after the appropriate therapeutic measures. The most serious effects invariably result from hyperthermia and rhabdomyolysis [100].

The diagnosis is based on the pharmacological and toxicological history and on the presence of the characteristic signs and symptoms [101]. Pharmaco-toxicological analytical test can help to identify the agent/agents in cause, especially in case of unknown history and in cases of drug abuse [102].

Although serotonin toxicity presents (in its most severe manifestations) characteristics common to neuroleptic malignant syndrome (NMS) [103], it is possible to differentiate the two forms based on the pharmacological history and neurological manifestations. In serotonin toxicity, in fact, hyperactivity, clones, tremors

Table 18.23 Signs/symptoms of mild, moderate and severe serotonin toxicity

	Neuromuscular	Autonomic	Others
Mild	Akathisia Hyperreflexia Inducible clonus	Diarrhoea Tachycardia Hypertension	Insomnia Anxiety
Moderate	Sustained clonus Myoclonus Tremor	Hyperthermia Mydriasis Diaphoresis	Agitation
Severe	Respiratory failure Rigidity Rhabdomyolysis	Severe hyperthermia	Confusion Stupor

and hyperreflexia are present, while in NMS bradykinesia and muscle stiffness are characteristic [101].

The clinical management and treatment are based on:

- Supportive measures (and intensive care in severe cases)
- Analytical monitoring of organ damage indices (e.g. CK, myoglobin)
- Muscle relaxation and treatment of myoclonus with benzodiazepines
- Cooling with ice, cold water, cooling blankets
- Specific treatment with the serotonin antagonist cyproheptadine per os (12 mg first administration, followed by 4 mg/h for four doses: the treatment can be prolonged), or, in alternative, with i.v. administration of chlorpromazine (25–50 mg).

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is an infrequent, but potentially lethal, neurological emergency. NMS can occur during treatment with neuroleptics (0.02–2.5% of patient taking neuroleptic medications) or for withdrawal of dopamine agonists, such as in Parkinson's disease patients [104]. Predisposing factors and mechanism underlying clinical manifestation are numerous and not completely understood, but the inhibitory effect on dopamine D2 receptors is always involved. A central deficiency of dopaminergic neurotransmission at nigrostriatal, mesolimbic and hypothalamic-pituitary pathways appears pivotal. However, peripheral mechanisms involving altered skeletal muscle mitochondrial function may also be involved [105].

NMS main **clinical manifestations** are [106]:

- Hyperthermia above 38 °C (100 °F) that can exceed 41 °C (106 °F)
- Muscle rigidity due to the involvement of the dopaminergic basal ganglia:
 - The main symptom is lead pipe rigidity with resistance to passive movement
 - Extrapyramidal movement disorders, tremors, bradykinesia, akinesia and hypomimia are often also present

- Rhabdomyolysis (creatinine kinase elevation at least four times upper the normal value)
- Mental status alterations including confusion, delirium and stupor up to coma. Catatonic agitation has been rarely described as feature of onset
- Autonomic changes and instability, such as hypertension or hypotension, cardiac diaphoresis, sialorrhea, pallor, urinary incontinence
- Hypermetabolic state with tachycardia and tachypnoea.

The diagnosis is clinical, and is based on a high index of suspicion, on the presence of characteristic signs/symptoms, and on the history of taking of one or more neuroleptic agents [107]. Elevation of CK is possible, and leucocytosis is common.

The goals of the **treatment** are [108, 109]:

- Supportive measures, intensive care and continuous monitoring of the body temperature
- Muscle relaxation: benzodiazepines, dantrolene, neuromuscular blocker (avoid succinylcholine)
 - Dantrolene administration: 1 mg/kg rapidly i.v., repeated as needed every 5–10 min to a maximum total dose of 10 mg/kg
- Cooling with ice, cold water, cooling blankets (antipyretics such as acetaminophen and acetylsalicylic acid are frequently ineffective)
- Specific treatment is possible with dopaminergic receptor agonists (e.g. bromocriptine, amantadine, cabergoline)
 - Bromocriptine administration: 2.5–10 mg orally or by gastric tube 3–4 times daily. Average adult dose is 5 mg every 8 h that could be increased to a maximum of 20 mg every 6 h

Lithium Toxicity due to Chronic Overmedication

Lithium is a cation principally used for the treatment of bipolar depression and other psychiatric disorders. Although lithium has been used therapeutically for more than 60 years, the precise

pharmacology of its therapeutic effects has not yet been fully elucidated: several mechanisms of action are hypothesized [110]:

- Effect on second messenger systems with inhibition of inositol monophosphatase and inositol depletion
- Reduction of protein kinase C activity, altering neurotransmission through effects on genomic expression
- Stimulation of neurogenesis through indirect actions on neural growth factors
- Enhancement of serotonin activity by several mechanisms, including increased synthesis of the neurotransmitter, inhibition of presynaptic serotonin 5-HT_{1A} autoreceptors and down-regulation of postsynaptic 5-HT₂ receptors
- Facilitation of norepinephrine release and enhancement of glutamatergic activity

Lithium is primarily a neurotoxin, whose neurotoxicity does not correlate with serum concentrations.

Lithium exposure can be divided into three main categories of toxicity:

- Acute toxicity: the toxicity depends on the rate of absorption and distribution.
- Chronic toxicity: the patient has a stable body burden of lithium when serum concentration is maintained in the therapeutic range, but this gentle equilibrium is changed by small perturbations, either by enhancing absorption or, more commonly, decreasing elimination: even a minimal alteration of the equilibrium between intake and elimination may lead to toxicity.
- Acute-on-chronic toxicity: the patient ingests an increased amount of lithium (intentionally or unintentionally) in the setting of a stable body burden. With tissue saturation, any additional lithium leads to signs and symptoms of toxicity.

Serious toxicity is most commonly caused by chronic overmedication in patients on stable therapeutic doses with renal impairment. Any state that causes dehydration, sodium depletion or excessive sodium reabsorption may lead to increased lithium reabsorption, accumulation and possibly intoxication, especially in ancient patients [111]. Acute overdose, in contrast, is generally less severe.

Lithium enters cells and substitutes for sodium or potassium: it is thought to stabilize cell membranes. With excessive levels, as in accumulation cases, it depresses neural excitation and synaptic transmission.

Acute ingestions of lithium-containing preparations produce pre-dominant early gastrointestinal symptoms (nausea, vomiting and diarrhoea), dehydration and dizziness, and they may be orthostatic: neurologic manifestations are a late finding in acute toxicity as the lithium redistributes slowly into the CNS, whereas electrocardiographic abnormalities (such as T-wave flattening or inversion, prolongation of QT interval) and bradycardia are reported.

Patients with **chronic intoxication** usually have systemic manifestations on admission. Toxicity may be severe with lithium levels only slightly above the therapeutic ranges, or even in normal range [112]: the serum lithium level gives a snapshot of the blood lithium concentration but does not always reflect the lithium levels in the other body compartments. Typically, patients with chronic intoxication have elevated BUN and creatinine levels and other evidence of dehydration or renal insufficiency. The main **symptoms** of mild-moderate and severe intoxications are summarized in Table 18.24.

Recovery is very slow, and patients may remain confused or obtunded for several days to weeks. Rarely, cerebellar and cognitive dysfunction is persistent: this syndrome, sometimes called

Table 18.24 Signs and symptoms of lithium chronic intoxication

Mild to moderate intoxication	Neurologic: lethargy, muscular weakness, slurred speech, dysarthria, nystagmus, ataxia, tremor, hyperreflexia, choreoathetoid movements, clonus, fasciculations, rigidity and extrapyramidal effects Cardiac: T-wave flattening or inversions and depressed ST segments in the lateral leads
Severe intoxication	Neurologic: agitated delirium, confusion, stupor, coma, seizures, hyperthermia Cardiac: bradycardia, sinus node arrest, complete heart block

SILENT (syndrome of irreversible lithium-effectuated neurotoxicity), is a neurologic dysfunction caused by chronic/prolonged lithium treatment in the absence of prior neurologic illness that persists for at least 2 months after cessation of the drug. Cases of rapidly progressive dementia, similar to Jakob-Creutzfeldt disease, have occurred and are usually reversible.

Patients undergoing chronic therapy who acutely ingest an additional amount of lithium (either intentionally or unintentionally) are at risk for signs and symptoms of both acute and chronic toxicity.

Treatment of lithium intoxication is based on:

- Symptomatic care for obtunded patients
- Replacement of fluids in dehydrated patients
- Enhanced lithium elimination: this can be achieved through
 - Haemodialysis (possible lithium clearance 60–170 ml/min): it is indicated in severe intoxications with seizures or severely abnormal mental status and in anuric patients. Repeated dialysis may be necessary
 - Continuous venous-venous haemodiafiltration (CVVHDF) (possible lithium clearance 28–62 ml/min): this technique is of choice in severe poisoning treated in ICU
 - Forced diuresis: this technique slightly increases lithium excretion compared with normal hydration and is not recommended
 - Normal diuresis (normal renal lithium clearance 20–25 ml/min): it is able to ensure a slow and progressive elimination of lithium if the plasma levels of sodium and potassium are maintained at higher normal values to facilitate the elimination of lithium. This treatment is the best choice in chronic intoxication

The Role of the Poison Control Centre and the Toxicological Analyses

The poison centres (PC) are a specialized public utility health services "... responsible for providing specialist advice and advice on the diagnosis, prognosis, treatment and possibly prevention of

human poisoning" (EEC Resolution 1990). They make available, 24/7, a specialist medical consultancy for toxicological problems. The operating methods of the PC, based on the exchange of information by telephone without the possibility of intervening directly on the intoxicated subject, represent a unique example in the healthcare field and the first fully operating form of telemedicine. A dedicated staff of trained/specialized physicians carry out the medical-specialist activity at the PC, and the telephone contact with the PC is the method of choice for obtaining information regarding the medical management of intoxications.

The consultation of the PC by physicians, both operating in the emergency field or in other hospital departments, appears completely natural if we consider the heterogeneity of the substances potentially causing intoxication—estimated to be more than 11,000,000—and the difficulties that clinical toxicologists face to manage the diagnostic-therapeutic process merging chemical and clinical evaluations. Moreover, several clinical information from the medical literature regarding poisonings and intoxications are sometimes anecdotal and often contradictory. Conversely, the attempts to disseminate database and consultation tools for the toxicological emergencies entrusted to other specialist physicians have proved ineffective, as the databases have proved to be redundant with information for the management of simpler case, and by contrast, unusable cases in patients with difficult, atypical presentation or in mixed poisonings.

The use of consultation of the PC is not systematic or constant and is strongly influenced both by individual experience and by the type of intoxication that the physicians are facing. Overall, PC is consulted for about a third of all patients with suspected acute poisoning presenting in EDs.

On the other hand, problems such as drug information, adverse drug reactions or the effects of chronic or prolonged exposures are more rarely discussed with the clinical toxicologist, although the management of these situations fully falls within the specialist skills of a PC dedicated to the management of complex cases.

The relationship that is established between a specialist physician and clinical toxicologist is strongly influenced by the quality of the service rendered by the PC. The emergency physician and the neurologist need full-fledged clinical-toxicological advice, even if by telephone, whose clinical and experiential content is evident and fully adapted to the patient under examination ("tailor-made" assessment). The interaction and close clinical collaboration between the clinical toxicologist and the emergency physician/neurologist represent the winning strategy to optimize the use of resources and ensure the appropriateness of care. In assessing the individual clinical problem, it is necessary to take into account the peculiarities of the specific context, which include the organizational characteristics of the hospital, the possibility of carrying out emergency toxicological tests and the availability of antidotes that all together are essential needs for the correct patient management.

The reasons for interaction between emergency physicians/neurologists and clinical toxicologist are not exclusively represented by the consultancy for the "first-hour management". The continuation of co-management of the patient throughout the diagnostic-therapeutic path expands the contents of the collaboration between the specialists and allows to optimize the continuation of therapies, to prevent unnecessary hospitalizations or early discharge and to set up a targeted follow-up in patients at risk of developing sequelae.

Toxicological Analysis on Blood/Urine

In many cases, some routine tests of normal biochemistry and blood gas analysis can be usefully used in the diagnosis and management of acute poisoning. However, it is the determination of the quantity of the toxic substances absorbed and present in the body, through toxicological analysis, which can confirm the diagnostic suspicion and allow the correct application of antidote treatments (and, more rarely, of extracorporeal purification techniques), as well as the formulation of a correct prognosis regardless of the signs and symptoms currently present. Unfortunately,

specific toxicological diagnostics are still scarcely available in most EDs, where there are no specific toxicology services and/or dedicated laboratories.

Analytical toxicology tests can be qualitative, semi-quantitative or quantitative; each method has different fields of application and response times and variable reliability and accuracy and requires specific analytical skills.

The urine screening of some substances of abuse and drugs represents the most widespread and simple analytical toxicology test. In the face of some advantages, such as the limited cost and the ease of execution, there are numerous limits related, for example, to the low sensitivity (false negatives) for molecules belonging to the same category of drugs, and limited specificity (false positives), for cross-reactivity between drugs. A further disadvantage is given by the urine matrix: in fact, in urine (a) the positivity for drugs can be related to the simple intake of therapeutic doses, (b) the cut-off may not allow to detect toxic concentrations of some molecules belonging to the tested category, (c) the concentrations of the eliminated toxic agents are influenced by diuresis and renal clearance, and (d) some substances (e.g. drugs of abuse) remain positive in the urine for days after taking, even when they are no longer the cause of clinically detectable toxic effects.

In many cases, only the quantitative blood test has diagnostic utility: these are poisons (as the “lesional” agents) for which a dose-effect correlation is known, the knowledge of which has evident therapeutic implications, as in the case of paracetamol, salicylic, digoxin, theophylline, carbamazepine, phenobarbital, tricyclic antidepressants, methanol, ethylene glycol, lithium, boron, iron and various metals.

The availability of the analytical data, both qualitative and quantitative, cannot however be separated from its clinical evaluation: numerous factors, in fact, such as modality and time elapsed from the assumption, metabolic-kinetic interference (e.g. active metabolites) and toxico-dynamics, as well as the implemented treatments, condition their meaning.

Only few hospitals dispose of laboratories capable of ensuring urgent quantitative toxicological analyses of a significative variety of xenobiotics. A better availability and organization of urgent analytical toxicology services would undoubtedly be desirable in several countries, especially as regards the analysis of "lesional" poisons (e.g. glycols, metals, solvents) and new substances of abuse. To date, in few regions/countries quantitative toxicological tests on blood and urine are available in the emergency setting: the reference PC is however able to intercept the analytical needs of the individual case and to activate laboratories capable of carrying out the necessary toxicological tests.

Selected Antidotes Useful for the Treatment of Neurotoxic Effects

The antidotes are compounds that allow the improvement of the prognosis *quoad vitam* or *quoad functionem* of the intoxication. They therefore play a decisive role in the management of the intoxicated patient even when they are used in the context of a multidrug treatment and together with other supportive treatments.

Some antidotes are commonly used in clinical practice, and their therapeutic effects and side effects are widely known (e.g. naloxone, flumazenil); others are rarely used, and their existence and availability is often unknown, although in some cases they are real life-saving drugs.

The appropriate use of antidotes can be based (a) on the anamnestic data only, or (b) on the anamnestic data in association with the clinical picture, or (c) it may require the use of toxicological tests that document the severity of the intoxication.

The clinical efficacy of some antidotes is immediate: examples are naloxone and flumazenil, which act as specific competitive antagonists on the opioid and benzodiazepine receptors, respectively. For this selectivity of action, associated with safety of use, these two antidotes can also be used for the diagnosis *ex adjuvantibus* of

coma due to unknown cause. On the other hand, some antidotes can counteract only some of the toxic effects of a xenobiotic; therefore, if the dose of the poison is high, it is likely that the use of the antidote would not be fully effective.

The clinical efficacy of an antidote depends strictly on the time within which it is used. One example is the use of naloxone: the antidote maintains its ability to displace the opioid from the receptor, but if an anoxic brain damage has already arisen, its late use cannot allow a return *ad integrum* of the brain function. Similarly, antidotes that inhibit the formation of toxic metabolites are clinically useful when used before the toxic is metabolized. In fact, only the early use of ethanol or fomepizole in poisoning with ethylene glycol and methanol can prevent the onset of organ damage caused by the metabolites of these xenobiotics.

The correct use of antidote treatment in the management of the patient with acute intoxication therefore requires knowledge of both the effectiveness of the antidote and the correct moment of use. In some cases, the correct and timely use of an antidote can make it possible to avoid further, demanding and expensive diagnostic procedures. Antidotes useful to treat some neurotoxic effects and intoxications are reported in Table 18.25.

Table 18.25 Main antidotes useful in poisoning and intoxication that cause neurological toxic effects in the emergency setting

Antidote and route of administration	Main indication	Main mechanism of action
Ethanol, i.v.	Methanol, ethylene glycol	Competitive inhibition of alcohol dehydrogenase
Atropine sulphate, i.v.	Carbamates, organophosphates, nerve agents, cholinergic syndrome	Competitive antagonism on muscarinic receptors

Continued

Table 18.25 Continued

Antidote and route of administration	Main indication	Main mechanism of action
Methylene blue, i.v.	Methemoglobinemia-causing agents (e.g. nitrites)	Restoration of the normal haemoglobin status
Dantrolene sodium, i.v.	NMS and malignant hyperthermia	Inhibition of the calcium release from sarcoplasmic reticulum
Physostigmine salicylate, i.v.	Central anticholinergic syndrome	Reversible inhibition of acetylcholinesterase
Flumazenil, i.v.	Benzodiazepine	Receptor antagonism
Glucagon, i.v.	Beta-blockers	Intracellular cAMP increase
Idarucizumab, i.v.	Dabigatran inactivation	Monoclonal antibody
Hydroxocobalamin, i.v.	Cyanide	Link to cyanide to form cyanocobalamin
Naloxone, i.v., i.m., i.n.	Opioids	Competitive antagonist on opioid receptors
Sodium thiosulphate, i.v.	Cyanide	Conversion of cyanide in thiocyanate
Pyridoxine, i.v.	Isoniazid, hydrazine	CNS GABA levels enhancer
	Ethylene glycol	Conversion of glyoxylates metabolites to glycine
Vitamin K, i.v., i.m., oral	Warfarins	Activation of coagulation factors in vitamin K-dependent process
Bromocriptine, oral	Neuroleptic malignant syndrome	Dopaminergic agonist

Table 18.25 Continued

Antidote and route of administration	Main indication	Main mechanism of action
Cabergoline, oral	Neuroleptic malignant syndrome	Dopaminergic agonist
Calcium gluconate, i.v., cutaneous	Fluorides	Inactivation of fluoride
Cyproheptadine, oral	Serotonin syndrome	Antagonist effect on serotonin and histamine receptors
Chlorpromazine, i.v.	Serotonin syndrome	Antagonist effect on serotonin and histamine receptors
Dantrolene, i.v., oral	NMS	Inhibition of the calcium release from sarcoplasmic reticulum
Fomepizole, i.v.	Ethylene glycol, methanol	Competitive inhibition of alcohol dehydrogenase
L-carnitine, i.v.	Hyperammonaemia, liver toxicity and encephalopathy due to valproic acid	Levocarnitine incrementation
Octreotide, i.v.	Hypoglycaemia due to sulfonyleurea or quinine	Antagonism of the insulin release
Pralidoxime, i.v.	Organophosphates	Regeneration of AChE
Botulinum antitoxin, i.v.	Botulism	Toxin inactivation
Thiamine, i.v., i.m.	Ethanol, ethylene glycol	Wernicke encephalopathy and Wernicke-Korsakoff syndrome
Dimercaptopropane sulfonate (DMPS), i.v., oral	Mercury, lead, polonium, cobalt	Chelator
Glyceridase, i.v.	Methotrexate toxicity	Cytoprotectant, inactivation of methotrexate

Continued

Table 18.25 Continued

Antidote and route of administration	Main indication	Main mechanism of action
Black widow spider (<i>Latrodectus</i> spp.) antivenom	Black widow and <i>Latrodectus tredecimguttatus</i> spiders	Venom inactivation
2,3-Dimercaptopropane sulfonate (DMSA), oral	Arsenic, lewisite, mercury, lead	Chelator
Rabies vaccine	Rabies prophylaxis (pre and post-exposure)	Active immunization
Argatroban, i.v.	Heparin thrombocytopenia	Inhibition of thrombin
Blu di Prussia, p.o.	Caesium, thallium	Ion exchanger that increases the movement of thallium and caesium into the GI tract
Diethylenetriaminepentaacetic acid (Ca-DTPA, Zn-DTPA), i.v.	Americium, plutonium	Chelator
Penicillamine, oral	Copper (Wilson syndrome), mercury, lead	Chelator
Uridine triacetate, oral	5-Fluorouracil/capecitabine	Inactivation of toxic metabolites

i.v. intravenous, *i.m.* intramuscular, *i.n.* intranasal

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19. Neurological Emergency Services: A Case for Change to the Model of Care?

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Anna Cavallini, and Giuseppe Micieli

Background

Neurological disorders are a common reason for admission to the ER; **these conditions, excluding stroke, account for 10–20% of emergency department (ED) attendances [1, 2].** Epilepsy, meningoencephalitis, Guillain-Barré syndrome, subarachnoid hemorrhage, primary and secondary headache and myasthenia gravis, as well as medical decompensation of chronic neurological disorders, such as: multiple sclerosis, dementia, and Parkinson's disease, may all lead to an emergency hospital admission. An Italian

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study, the *NeuDay Initiative* [3], in November 2018 surveyed Italian ERs that have access to neurological consultation; as expected the most common reason for requesting neurological consultations was cerebrovascular diseases (23.6%), followed by headaches (12%), head injuries (8.6%), dizziness (7.7%), transient disturbances of consciousness (7.1%), epileptic seizures (6.6%), delirium or confusional state (2.7%), other mental disorders (2.6%), as well as less frequent pathological conditions such as Guillain-Barré syndrome, meningoencephalitis, and others that would account all together for approximately 12.0% of all accesses.

It follows that some of the neurological conditions for which PS support is requested may not have the specific requirements of the pathological conditions for which hospitalization is appropriate.

Conversely, it is likely that many conditions, especially of a transitory nature (cerebral ischemic attacks, short-lived and new-onset symptomatic headache forms, stroke mimic with changes in alertness and behavior, rather than focal critical episodes) may not be perceived how effectively urgent and their evaluation is delayed by hours or days often with the use of a general practitioner or even territorial specialists.

Compared to other patients in the emergency room, **patients** who present **with neurological symptoms are** more often **seriously ill** – this is shown by high rate of emergency procedures and services required by this population as well as the fact that a high proportion of patients presenting with neurological complaints have to be admitted to the hospital. It has been demonstrated that 76% of the neurological emergencies involved vital risk and/or potential life risk, compared to 61% of emergencies due to medical pathology [4].

Almost 50–90% of patients discharged by neurology departments are admitted via the emergency room. The patient population varies depending on the location (regions), structure of the respective emergency room, and the local referral concepts that have grown over decades.

The spectrum of neurologic emergencies that are encountered in the emergency department is wide, and treatment modalities

and interventions are evolving at a rapid pace. Accurate and timely diagnosis is critical in these patients because many treatments are time dependent and crucial to the patients' long-term outcomes in terms of functional prognosis, quality of life, and autonomy in the activities of daily life. The expertise of the managing physician and the setting of the emergency room (ER) may also affect the outcome: acute neurology services provide cost savings in terms of admission avoidance, reduced length of stay, and a reduction in investigations requested [5]. Involvement of a neurologist leads to a change in diagnosis and management in up to 79% of patients [6]. Incorrect or delayed diagnosis can result in neurological permanent damage, poor clinical outcome for the single patient, with a significant impact in terms of functional, and socioeconomic burden. On the other hand, lack or limited availability of neurological expertise (sometimes provided only as formal/informal telephone advice) may lead to disproportionate volume of secondary care admissions compared to non-neurological, medical disorders [7], unnecessary redundant investigations [8], and in some cases increase of the time taken to establish definitive treatment [4, 9].

In 2011, the Association of British Neurologists (ABN) called for a 24-h target for patients to be seen by neurologists after referral [10] and recommended a neurologist consultant ratio for local adult neurology services to be 1 neurologist per 70,000 population.

Nevertheless, in the last decade, efforts to prioritize acute neurology service provision in Great Britain and in the rest of Europe have not reached the ABN recommended standard.

Disparities in access to emergency health care for the neurology specialties are well-known and well-documented [9]. These disparities are due to:

1. **Shortage of neurologists at a global level**
2. **Limited number/access to neurology training programs between countries of various income groups**
3. **Suboptimal organization of neurology emergency care**

Shortage of Neurologists at a Global Level

Although **there are 5.14 neurologists per 100,000 population in high-income countries**, there are only **0.032 neurologists per 100,000 population in low-income countries**, many of which do not have a single neurologist at all. For example, in **Africa**, there are on average only 0.06 neurologists per 100,000 people. High-income countries are experiencing a shortage of neurologists as well, with the most critical need occurring in acute care settings. A report by the **USA's** National Center for Health Workforce Analysis estimates that while the supply of US neurologists may have grown by 11% between 2013 and 2025, demand will have grown by 16%. **Europe** also faces problems of regional imbalances, with the most critical need occurring in acute care settings. Advances in treatment for neurological conditions and longer life expectancy increase the demand for neurology services: as life expectancy increases, more people develop neurological conditions such as Parkinson's disease, Alzheimer's, and other types of dementia that are significantly more common in the elderly than in the general population; these condition, even if chronic, may lead to ER visits for disease decompensation, medical secondary complications, and neurologist consultation would most likely requested by the ER physician to have a better understanding of the clinical pictures, therapeutic interventions, and follow-up.

Limited Number/Access to Neurology Training Programs Between Countries of Various Income Groups

Concerning the **training in Neurology** WHO data provide the median number of postgraduates specializing in neurology per year per 100,000 people for each income group [2]: 0 in low-income countries, 0.04 in lower-middle-income countries, 0.07 in upper-middle-income countries, and 2.96 in high-income countries. Many of the more recent studies provide the total number of neurology trainees per 100,000 people with medians of 0.02, 0.10, 0.27, and 0.54 for the respective income groups. A recent review has summarized the worldwide distribution of neurology training programs, the characteristics of training programs and curricula in the

different parts of the world, and initiatives aimed at increasing access to neurology training in under-resourced regions [11]. It has pointed out significant differences in competency levels of relevant skills to the emergency neurology, such as the ability to perform lumbar puncture, evaluation of CT/MRI, neurointensive care, performing ultrasound/Doppler, evaluation of EEG, and basic CSF diagnostics.

Suboptimal Organization of Neurology Emergency Care

While for the case of cerebral stroke, there are now significant and almost unchallengeable evidences that dedicated stroke care (the stroke unit model) offer clear benefits over “non-dedicated” care in terms of long-term disability and mortality, the optimal way to manage other acute neurological emergencies is not yet established even though they account for 20% [1] of all non-stroke acute medical admissions.

It could be argued that **identifying the stroke unit as the only high-level neurological healthcare component of the emergency setting has limited the neurological expertise only to stroke patients** [12]. Patients with high care burden disorders such as Guillain-Barré syndrome, encephalitis, myasthenia gravis crisis, acute confusional states, epileptic seizures and status epilepticus, “urgent” headaches, vertiginous syndromes, transitory impairment of consciousness require medical and nursing specialized care pathways, and neurological expertise. Those patients (as stroke patients do) would probably benefit from a dedicated environment within emergency setting.

Models of Care

The organization and management of neurological emergencies differs among hospitals, with some hospitals having interdisciplinary ERs with consulting neurologists. Others have specialized neurological ERs. In some hospitals, a neurologist is not available and patients are often treated by internal medicine specialists and are referred to tertiary centers if necessary.

As the demand for neurological care far outweighs its accessibility, the use of telemedicine is a possible and effective option to optimize neurological resources in both emergent and non-emergent settings [13]. Stroke care via telemedicine paved the way for other telemedicine services; telestroke services are components of stroke models of care for >10 years in many countries [14].

Telestroke has contributed to expand access to care, improve quality of stroke management and timeliness of care, increase treatment rates for reperfusion therapy in patients with ischemic stroke [13]. In addition, there are substantial evidence that the use of telestroke does not increase the number of stroke mimics compared to in-person evaluations, suggesting that stroke assessment scales such as NIHSS [15] and imaging interpretations are equivalent between in-person and telestroke evaluations [16]. There are studies demonstrating telestroke efficacy with a wide range of technologies, such as smartphone [17] and tablets. Telestroke is in use in many countries and is accepted among patients with different cultural background. Telemedicine as a tool by which we can deliver care in neurology emergency setting has been less developed; nonetheless evidences from studies and observations across multiple specialties report non-inferiority of evaluations by telemedicine compared with traditional, in-person evaluations in terms of patient and caregiver satisfaction, improved access to care, diagnostic accuracy, improved outcomes, and cost savings for individual users and health system use [13]. There are limited examples of the use of teleneurology in emergency setting, a recent study [18] describes 14 years activity of regional rural French telemedicine network, dedicated to medical and surgical neurological emergencies. The study describes the activity of eight community hospital emergency departments remotely connected to the only university hospital in Franche-Comté, France. From 2002 to 2015, 23,710 patients received telemedicine consultations for acute neurology conditions, not surprisingly the remote consultation was for stroke in 30% of cases, head or spinal injuries in 36%, and cerebral tumors 9%. As expected the use of telemedicine increased the rate of acute ischemic stroke patients who received thrombolysis, 33.5% of the procedures were performed with remote consultation. Almost 75% of patients admitted to the community hospitals that

did not have onsite neurological expertise had received could benefit of neurological expertise for the use of teleneurology consultations. In these model apart from clinical benefits due to timely access to neurological expertise in the acute phase, economic savings came from the reduction of unnecessary secondary interhospital transfers.

In 2016 the subcommittee Neurological Emergency Medicine of the German Neurological Society conducted an online survey to investigate the organizational structures of emergency neurology in Germany [19]. The proportion of inpatients admitted to hospitals via emergency departments amounted to 78% (median) in general nonacademic hospitals and 52% in university hospitals. The survey results revealed that **most emergency departments are organized as an interdisciplinary structure combining medical with surgical disciplines frequently led by an independent department head** (that could also be neurologist!).

Neurology departments employ rather diverse strategies to organize neurological emergency care: the most common model (present in around 50% of the structures that answered the questionnaire) for the integration of neurological expertise in the emergency department for all types of hospitals is the care of emergency neurological patients by emergency physician; in 15% of cases, the neurologist would be called for emergency neurological cases as a consultant. A university clinic stated that neurologists were not involved in the emergency room at all, although the complexity and the variety of the different service models are extremely broad. Neurologists are involved in different ways in the emergency room in the largest hospitals, a separate neurological emergency room is very rare. As an important part of neurological emergency care, all university hospitals and the vast majority of the other hospitals with a neurology department have a specialized stroke unit; separate neurological intensive care units are also present in university hospitals (59%) but less represented in General hospital (11%). Specific standard procedures were available for stroke in 82% of respondent hospitals, but only in 4% of hospitals, a protocol/clinical pathway for coma was present. Most of the patients presenting with neurological emergency arrive with ambulance, around 25% are self-referral or

referral by a general practitioner or family doctor. According to the respondents, around two thirds of all neurological emergency were appropriate, whereas in a lesser percentage of cases, the patient had turned to the emergency room for a neurological consultation because a timely outpatient appointment was not available.

One possible model to address neurological emergencies is to set up an **hyperacute neurology unit (HANU) analogous to the stroke model**; pilot studies were carried out in two London hospitals for a period of 6 weeks in 2015 in order to evaluate whether the introduction of this model could contribute to a more responsive and clinically effective service for patients who attend the emergency department or were admitted with an acute neurological condition [20]. There were two different models of acute neurology implemented during the pilot. In the first model, patients were seen within 4 h of their arrival, and if they did not require admission, they would be discharged directly from emergency department and followed up appointments in dedicated clinic. Those who required admission would be admitted to one of the two acute medical wards. In the second hospital, neurological emergency team would take referrals directly after triage; patients would be seen while still in ED, within 30 min from the time of referral. Those who required a fast evaluation would be admitted, either under the care of a neurology consultant or a medical consultant on acute medical unit. There was also capacity within the acute neurology service to rapidly follow-up patients as outpatients using a dedicated room in ambulatory care. The findings from the HANU study suggest that the model may have a broad array of benefits arising from prompt access to neurology consultation in the ER:

1. Rapid diagnosis and discharge reducing the potential for inappropriate medical admissions
2. Increased neurological support in the emergency department empowering communication among emergency health personnel and peer learning
3. Facilitating patient flow with quick referral to right specialist
4. Improvement of the patient experience of care and satisfaction by providing timely diagnosis and appropriate management plan
5. Reduced readmissions and emergency department visits
6. Early neurology evaluation is critical to identifying uncommon or complex disorders that are not recognized by non-neurologist

specialists particularly at the time of acute onset and may therefore provide for timely diagnosis, appropriate care plan and improve prognosis

The greatest benefits were observed secondary to specialized consultancy for patients in the acute medical unit and emergency department rather than by the “ownership” of inpatients, as admissions were in any case substantially reduced [15].

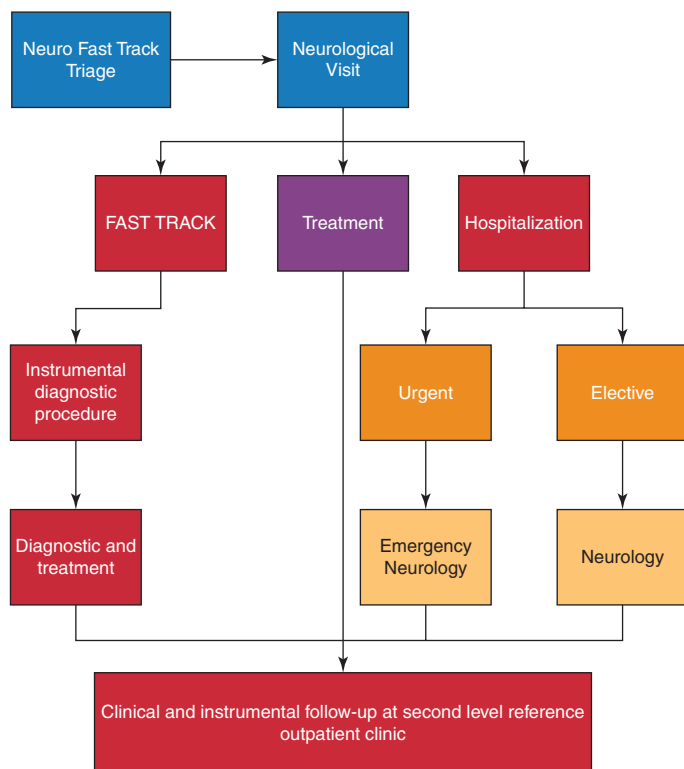
In 2016 [21] the hyperacute neurology service (HANS) structured on the traditional “hub-and-spoke” model of regional neuroscience centers and allied acute district general hospitals was proposed to expand acute neurology service provision in London [15] using the existing stroke care infrastructure that has already proven improved outcome and reduced costs, and which has many synergies with other neurological conditions [15]. St George’s Hospital hyperacute neurology service has experienced a successful working model for this interaction [16]. The HANS become a comprehensive, consultant-delivered service set in a teaching hospital regional neuroscience center. The service adopts a comprehensive diagnostic approach to acute neurology, prioritizing the emergency department management of both stroke, stroke mimics, and neurological emergencies, through active daily support to the emergency department and to the acute medical.

The organizational model includes also rapid access to clinics to assess ambulatory patients, allowing a reduction of the referrals from primary care to acute setting. Comparing the **traditional model of neurology liaison** to the **hyperacute neurology service** the following significant results were observed after 1 year:

1. All patients referred to neurologist received a consultant review (100% vs 77.2%) [16]
2. Shortening of time to review: from 2-day median (3.9–18.0 interquartile range—IQR) to 0 day (1 IQR) [16]
3. 25% of the cases reviewed by a neurologist in the emergency department were discharged [16]
4. Reduction of time from review to discharge: from 4.0 day median (1.0–11.8 IQR) to 0.0 day median (0.0–3.0 IQR) [16]
5. Improvement in the length of stay for non-stroke disorders [22]
6. Occupancy of stroke beds by non-stroke cases was reduced by 50% [16]

The **Neuro Fast Track (NFT)** active at the Mondino Hospital, Pavia, **Italy**, is a very interesting and promising model with high potential in increase the quality and appropriateness of timely care, improve patients prognosis and reduce unnecessary admissions and exams. NFT Mondino is a project aimed at managing patients with urgent neurological conditions, which are not channeled through the hospital emergency department (Fig. 19.1 describes access, screening, and paths in Neuro Fast Track). In this model, the identification/selection of patients with urgent neurological conditions is performed by the general practitioner, a specialist clinic, the ER specialist, or the consultant neurologist. NFT will then perform

Figure 19.1 Access, screening and paths in Neuro Fast Track



patient's admission and planning of the necessary diagnostic tests and treatments in a dedicated context

Nowadays the patient with a neurological condition in "deferrable urgency" (to be evaluated in the following 72 h) can be:

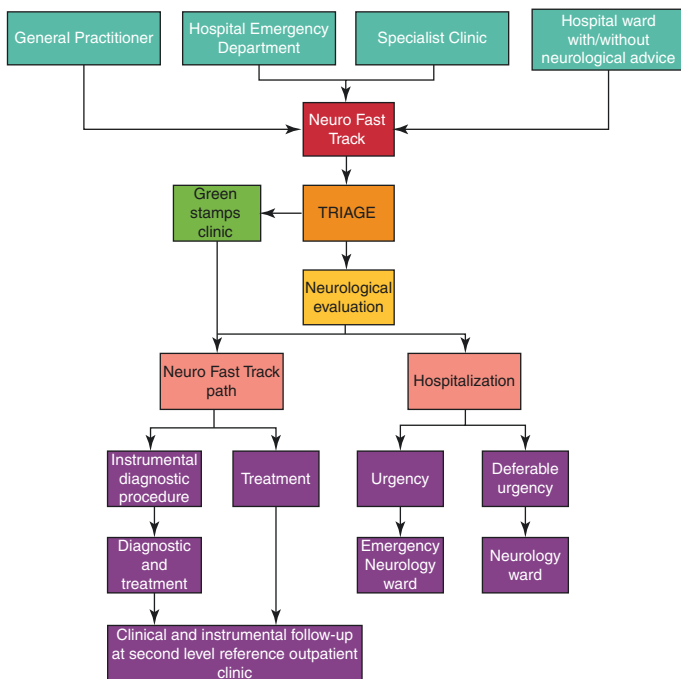
- Sent to the hospital by a general practitioner or specialist clinic
- Managed in the ED, without direct hospitalization, with prescribed follow-up to be organized by the patient
- Managed in other clinics or wards in the same hospital, where a neurological consult is requested

As a result, delayed diagnosis, incomplete case management, and inappropriate hospitalizations are frequently observed. NFT, inspired by the American Acute Neurology Clinic model, aims at redesigning the admission process for "urgent" patients to achieve an effective and efficient screening of the cases, an improved planning of the diagnostic investigations and their subsequent reassessment, a prompt execution of the required tests, and the prevention of inappropriate hospitalizations.

NFT model (Fig. 19.2) implemented in Mondino Hospital in Pavia is based on key organizational foundations:

- The centralization of the decision-making process in the neurology ward, to be managed by staff with 10+ years of experience with urgent neurological conditions.
- The identification of a dedicated space for Neuro Fast Track in proximity with admission and administrative services (such as Triage, Clinic, Nurses' area, ICU, infusion therapies, and waiting rooms).

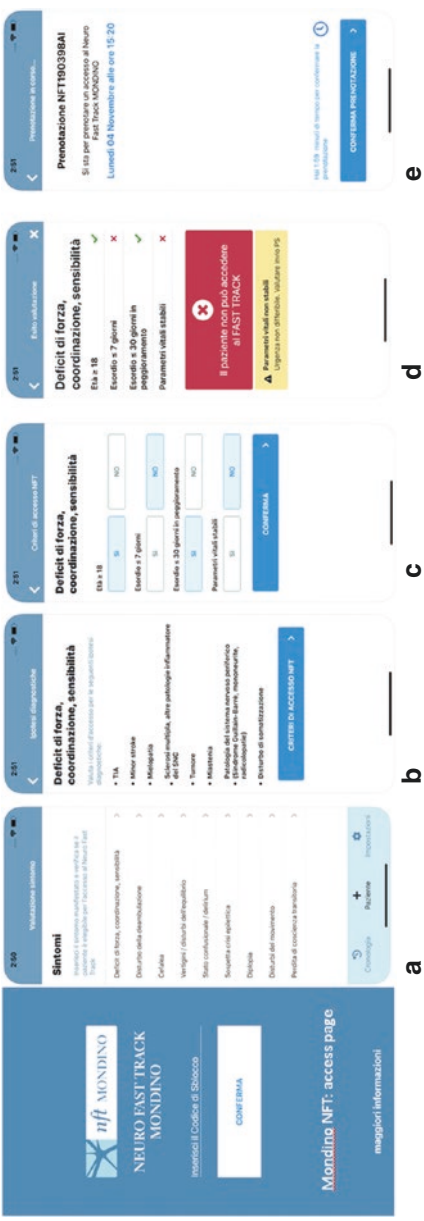
Criteria for admission to NFT are established to accelerate the decision-making process and the initiation of tests and treatments. The Mondino NFT uses a dedicated App, developed for iOS and Android, to enhance and facilitate the implementation of the activities. The App (Fig. 19.3) collects privacy consent and personal medical data, allows diagnostic tests booking, and provides short reports to facilitate the overview of all details. Family physician is connected with Mondino FT and has real-time overview of calendars and patients activities.

Figure 19.2 **Organizational model of Mondino Neuro Fast Track**

Unmet Needs: A Case for Change

The recognition of neurology as an essential component of emergency care is evident from the intensive involvement of neurologists in interdisciplinary treatment. Till today most efforts have focused on stroke care and the existing models of care of the stroke unit, stroke network and the investment in telestroke and in technologies have empowered timely access to stroke expertise, improved patients prognosis and functional outcome, and reduced the burden of inappropriate admissions. As it already happens for stroke, greater specialist involvement in acute neurological presentations and dedicated clinical pathways is likely to improve patient outcomes, limit unnecessary admissions, and reduce the economic burden of acute neurological condition both at disease onset stage and acute on chronic phase.

Figure 19.3 Mondino Neuro Fast Track APP. (a) symptoms, (b) diagnostic hypothesis, (c) access criteria to the NFT, (d) access criteria to the NFT not fulfilled patient is directed to ER, (e) access criteria to the NFT fulfilled: patient is booked for neurological consultation



This case for change proposes that patients with a primary acute neurological conditions are systematically reviewed and managed by neurology specialists in acute settings through the development of acute neurology standards and models.

Considering the wide range of overlapping issues among stroke and acute neurological conditions and that non-stroke conditions admitted via stroke pathways comprise a significant cohort, it would be advisable to build emergency neurology care on the already existing infrastructure (models, pathways, dedicated environment, competences) for stroke care. Nonetheless how best to integrate existing hyperacute stroke and acute neurology resources remains an issue [22].

The increasing importance of the care of neurological emergencies also has its economic side. The proportion of neurological emergencies in practices, but especially in hospitals, is steadily increasing. Many clinics are already treating emergencies predominantly, so that the spectrum of neurological diseases in hospitals and training centers is shifting, with all the advantages and disadvantages for training, as well as the infrastructure and staff to be maintained.

Sustainable and needs-based cross-sector care concepts should be developed to facilitate this structural and cultural integration transforming services and orienting them to current patient needs. Just as in stroke medicine, which has gained significant impetus from the scientific work of neurology in the past few decades, neurological emergency medicine must also receive greater scientific attention: academic curricula and postgraduate medical education should be tailored on current clinical and organizational challenges.

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